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Parity and the use of folic acid supplementation during pregnancy

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ABSTRACT

Objective Folic acid (FA) supplementation has long been recommended before and during pregnancy to reduce the risk of neural tube defects. Factors influencing adherence to FA supplementation have been extensively evaluated, but little is known on the effect of parity. This study comes to examine the association between parity and maternal use of FA prior to and during pregnancy.

Methods In this retrospective population-based study, we identified mothers (N=228 555) of all children (N=578 204) born between the years 2000 and 2016 among members of a large health provider in Israel. Data on FA supplementation purchases were obtained from centralised medical databases.

Results The median (IQR) total dose of FA purchased 12 months prior to child birth among previously nulliparous women (120 mg, 48–240) was significantly (p<0.001) higher than the dose purchased by women with one (90 mg (39–202)) and two prior births (84 mg (36–182)). The dose was even lower in women for three or more prior births (75 mg (36–165)). Despite the overall increasing secular trend in FA purchases during the study period, the negative relationship with parity remained.

Conclusions Adherence to FA supplementation is negatively associated with parity. Women with increasing parity may be at higher risk for pregnancy complications associated with low FA levels. The results of this study may inform the design of interventions to specifically increase adherence to FA supplementations among multiparous women.

Folic acid (FA) supplementation has long been recommended before and during pregnancy to reduce the risk of neural tube defects (NTDs).[1–3] A series of observational and interventional studies have found that FA supplementation of the recommended daily dose (400 µg) can prevent up to 72% of NTDs.[4–6] Subsequently, the Food and Drug Administration has mandated programmes for fortification of grain-based food with FA[4 7] in the USA, where flour has been enriched since 1996 to provide an estimated of 100–200 µg of FA supplementation per day to women of childbearing age. While many countries implemented similar enrichment programmes, no such programmes currently exist in the EU or in Israel.[8]

Nutritional folate consumption is not sufficient for optimal reduction of NTD risk, therefore many countries encourage women to take an FA supplement from 3 months before conception and during the first 12 weeks of pregnancy.[6] In Israel, the Ministry of Health (MoH) currently recommends doses ranging from 400 µg/day to 800 µg/day for low-risk pregnancies to as high as 4000 µg/day for high-risk pregnancies (such as those with a previous NTD).[5 9] A 2012 report suggested a 22% reduction in NTDs rates in Israel after the release of these MoH recommendations in 2000, from 11.7 cases per 10 000 live births in 1999 to 9.1 cases per 10 000 births in 2010.[10]

FA supplements and prenatal vitaims in Israel are subsidised by the government through the National Health Insurance Act and are available to all women at low cost. Nonetheless, adherence with FA supplementation before and during pregnancy is relatively low with only 39% of Jewish women adhering to the recommendation.[11] The issue of low adherence with recommendations is of particular concern in unplanned pregnancies. According to one study,[12] only 7% of childbearing women who did not plan their pregnancy have taken preconception FA supplementation for the recommended 12 weeks. Several sociodemographic factors have been found to affect adherence with FA supplementation during pregnancy, including maternal age, socioeconomic status (SES),[13] level of education[14] and immigration status.[15] Parity has been shown to be negatively associated with adherence in several previous studies, but these were limited to self-reports[16–18] and selective study populations.[19] Studies were also limited to small number of multiparous women. For example, in a national survey among all maternity units in France, only 7% of interviewed women had a parity of 3 or above.[20] In this study, we aimed at objectively examining the association between adherence with FA among

pregnant women in Israel, a society characterised by high fertility rates.

METHODS

Data source

We used the computerised databases of Maccabi Healthcare Services (MHS), a 2.2 million member not-for-profit care provider, which provides health services to 25% of the total population in Israel. According to the National Health Act, MHS may not exclude applicants on any grounds, including age, state of health or religion. Therefore, all subpopulations are represented in the database, and MHS members have an age distribution similar to the general population. The MHS database integrates data from the MHS central laboratory, medication purchases throughout the MHS pharmacy network, physician consultations, hospitalisations, procedures and sociodemographic data since 1998. This method obviates the bias associated with retrospective self-reporting.

Study population and design

In this retrospective cohort study, we identified the mothers of all live births between the years 2000–2016. The index date was defined as the child's day of birth. To be included in the study, mothers had to have been continuously enrolled in Maccabi for at least 12 months before the index date. Written informed consent was not required as this study was a retrospective database analysis, and all data were anonymous.

Assessment of exposure to FA during pregnancy

We identified all purchases of FA supplementation from MHS databases, including dose and number of packs for 12 months before the index date. While FA supplements could also be purchased over the counter outside MHS, the cost is lower (eg, $5 compared with $12 for 100 tabs of 400 µg) if the purchase is made within the system.

Study variables

Study variables included age of mother, region of residence, parity, calendar year at index and SES. SES was based on the poverty index of the mother's enumeration area, as defined by Israel's 2008 national census. The poverty index is based on several parameters including household income, educational level, crowding, physical conditions and car ownership.[21] We also collected information on the following comorbid maternal conditions at index date using MHS's patient registries[22 23]: diabetes mellitus, hypertension, cardiovascular diseases, cancer and subfertility. In addition, we collected data on smoking status (ever, never and unknown) as documented in the electronic medical record.

Statistical analysis

Descriptive statistics were calculated for all variables of interest and compared using χ^2 tests for categorical tests and the non-parametric Kruskal-Wallis test for continuous variables. Median and IQR total dosage of FA purchased in the 12-month period before birth of each child were calculated and compared by parity. Mean cumulative doses are also presented and adjusted for age of mother at birth of the child, SES and year of birth of the child after log transformation of original values.

Additionally, FA supplementation is considered most effective at preventing NTD during first trimester of pregnancy; therefore, we performed a sensitivity analysis in order to check the amount of FA that was purchased during these months and 3 months before onset of pregnancy. Log transformation was used to reduce variability for the FA dose, and outliers were excluded (included: log≥1 and log≤3). All analyses were conducted using IBM SPSS Statistics for Windows, V.22.0, and a p value<0.05 was considered statistically significant.

RESULTS

The study population consisted of 578 204 children and 228 555 mothers. The mean age of women on their first birth was 29.34 (SD=5.52), 37.7% of the women had their first birth before the age of 27 years, while 17.6% of the women had their first birth after the age of 35 years. The majority of women lived in the centre of the country (67.3%) and more than half of the women had a medium to high SES (66.7%, table 1).

Overall, 18.6% of women did not purchase FA at all in the year preceding birth of their child, with this value being lower for women with no previous live births (14.2%) and higher for those with parity ≥3 (25.2%, table 2).

The median dose of FA purchased 12 months before the birth of the first child during the study period (120 mg, IQR=48–240) was significantly higher than the dose purchased 12 months before the birth of the second and third child (90 mg, IQR=39–202 and 84 mg, IQR=36–182 respectively; p<0.001). For the fourth birth and over, the dose was even lower (75 mg, IQR=36–165, table 3). The dose reported is the total dose in mg purchased for the whole period; therefore, for nulliparous women, the median daily dose was 120/365=0.328 mg.

Parity was negatively associated with FA purchases even after stratification by mother's age at index date (figure 1), and similar results were found with stratification by calendar years (2000–2005 and 2006–2016, table 4).

When restricting the analysis to cumulative purchases during the first trimester (n=311 104), the total median FA dose for the nulliparous women was 48 mg (median daily dose of 0.526 mg) and the amount of FA purchased decreased as parity increased (data not shown).

DISCUSSION

The study results clearly indicate a significant negative association between parity and adherence to FA supplementation purchases among pregnant women. This is in agreement with several previous studies. Surén *et al*

Table 1 Study population characteristics at index date, for all mothers at the birth of their first child

	N=**228 555 (n (%))**
Year of child birth	
2000–2005	108 475 (47.5)
2006–2016	120 080 (52.5)
Age (years) of mother	
≤27	86 243 (37.7)
28–31	69 295 (30.3)
32–34	32 799 (14.4)
≥35	40 218 (17.6)
District	
Center	153 862 (67.3)
North	39 139 (17.1)
South	35 554 (15.6)
Socioeconomic status*	
1–5	76 114 (33.3)
6	47 279 (20.7)
7–10	105 162 (46.0)
Smoking	
Never	200 122 (87.6)
Ever	20 488 (9.0)
Unknown	7945 (3.5)
Comorbid conditions	
Cardiovascular	2486 (1.1)
Diabetes mellitus	1070 (0.5)
Hypertension	2232 (1.0)
Cancer	1507 (0.7)
Fertility register	42 389 (18.5)

*Scale between 1 (lowest) to 10.

showed that as parity increased, the proportion of mothers consuming FA decreased: among previously nulliparous women, 44.6% of pregnant mothers consumed FA, compared with 19.4% of mothers with two or more prior births.[24] Similar results were reported by another study

Table 2 Comparison of mothers who purchased at least once or did not purchase FA within year before birth of each child, by parity

Parity	No purchases (N=107 278) (n (%))	At least one purchase (N=470 926) (n (%))	P value
Nulliparous	33 731 (14.2)	202 999 (85.8)	<0.01
1	37 624 (20.0)	150 762 (80.0)	
2	20 377 (22.3)	71 090 (77.7)	
≥3	15 546 (25.2)	46 075 (74.8)	

FA, folic acid.

Table 3 Folic acid supplementation (total mg) purchased by mothers for the 12-month period to birth of child, for those with at least one purchase of FA and excluding outliers (p<0.001)

Parity	n	Median (IQR)	Ajdusted mean* (SD)
Nulliparous	199 664	120 (48–240)	251 (9)
1	149 197	90 (39–202)	195 (9)
2	70 499	84 (36–182)	132 (7)
≥3	45 749	75 (36–165)	117 (6)

*Adjusted for age of mother at birth of the child, socioeconomic status and year of birth of the child after log transformation of original values.
FA, folic acid.

that examined the association between mothers' use of prenatal FA and risk of severe language delay using self-reported questionnaires to determine FA use.[17]

Our results are also consistent with previous studies that have shown that nulliparous mothers had increased adherence to prenatal recommendations and healthcare utilisation compared with multiparous women, suggesting that women who have had a previous normal pregnancy may fail to recognise important elements of care in subsequent pregnancies.[25 26]

We additionally observed that during the 1-year period before birth, 18.6% of mothers did not have any purchase of FA. This is a significant improvement compared with previously published data from a national survey of 1860 women in Israel that showed that 61% did not consume FA before pregnancy[11] and is comparable with a self-reported study that reported 29% non-compliance.[27] Our

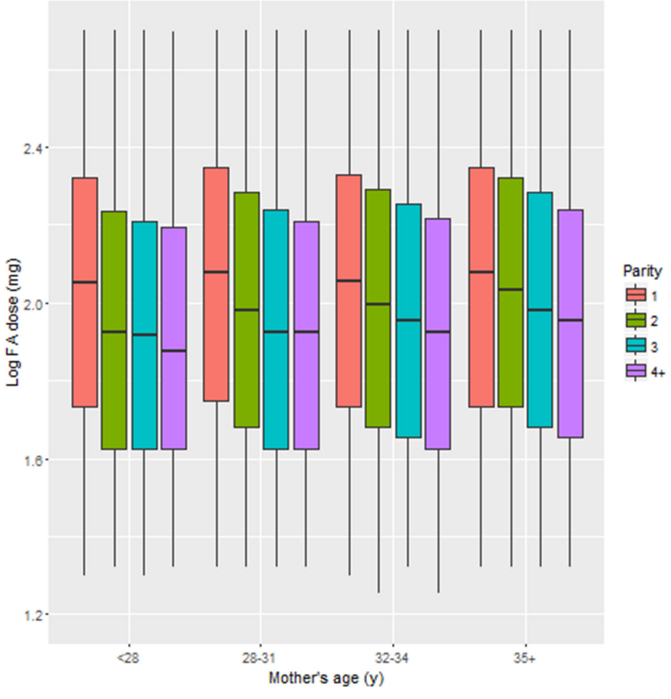

Figure 1 Log median cumulative dose of FA purchased by mothers for the 12-month period before birth, by mother's age, excluding outliers. FA, folic acid.

Table 4 Median cumulative dose (total mg) of FA purchased by mothers for the 12-month period before birth, by calendar year for those that purchased, and excluding outliers, n=465 109

Time period	Parity	N	Median (IQR)	P value
2000–2005	Nulliparous	94 144	90 (40.5–210)	<0.001
	1	53 284	75 (33–180)	
	2	12 502	63 (30–150)	
	≥3	3810	60 (30–147)	
2006–2016	Nulliparous	105 520	135 (60–270)	<0.001
	1	95 913	96 (42–210)	
	2	57 997	90 (36–192)	
	≥3	41 939	75 (36–168)	

result additionally indicates that adherence to FA supplementation in Israel is greater than has been reported in a number of other countries. A study from the UK observed that the percentage of women who did not consume any amount of FA before and during pregnancy increased from 65% in 1999–2001 to 69% in 2011-2012,[28] and other studies similarly estimated that 28%–50% of expectant women do not use FA supplementation.[17 24] Our observation of an increase in use of FA supplementation over time from the year 2000 confirms previous finding from a national survey in Israel[11] that indicated an increase in adherence from 5.2% of pregnant women in the year 2000 to 39% in 2005 following the release of the Health Ministry recommendation concerning FA supplementations.[29]

Nulliparous women received median daily dose of FA for the year before childbirth of 0.328 mg, in agreement with guidelines,[11 30] whereas multiparous women received suboptimal daily doses of FA, a finding that is observed globally.[31] Our analyses indicate that women with lower SES had decreased FA supplementation. Previous studies report similar results reflecting health inequalities in prenatal care for women with lower SES and ethnic minorities.[32] A systemic review reported that younger age, less education, higher parity and lower SES led to inadequate prenatal healthcare utilisation.[33]

In addition to its large study population, the strengths of this study are its long-term, historical prospective and systematic exposure assessment. Our study has the limitation that data were unavailable before 1998, leaving some uncertainty regarding parity status of women giving birth in early years. However, the calculated median maternal age at birth of the first child in our study sample (29.34 years) is similar to the one reported for the Jewish population in Israel (28.65 years) as reported by the Israel Bureau of Statistics,[34] suggesting that inaccuracy is probably minimal. Missing data about purchasing FA supplementation outside the network is another potential information bias in this analysis but seems to be non-differential and therefore should not have affected study conclusions, although may have negatively affected the median dose calculated in this study. Moreover, the proportion of non-compliance is relatively low suggesting that purchasing outside of the network is likely to be low. In addition, our analysis did not take into account interval between pregnancies that has been shown to affect preconception FA use.

CONCLUSION

Parity is negatively associated with adherence to FA supplementation. Further studies need to be carried out to develop interventions to increase adherence to FA supplementations, particularly in multiparous women.

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