Consumption of Folic Acid Supplement and High Dietary Folate among Nepalese Women during Preconception and Pregnancy in Association with Premature Birth: A Case-Control Study

การรับประทานกรดโฟลิคและอาหารที่มีโฟเลทสูงในสตรีชาวเนปาลระยะก่อนตั้งครรภ์และระยะตั้งครรภ์ที่มีความสัมพันธ์กับการคลอดก่อนกำหนด: การศึกษาแบบมีกลุ่มควบคุม

Binita Puri, M.S.N.[1] Wannee Deoisres, Ph.D.[2]* Wantana Suppaseemanont, Ph.D.[3]
Binita Puri, M.S.N., วรรณี เดียวอิศเรศ, Ph.D., วรรณทนา ศุภสีมานนท์, Ph.D.

Abstract

This case-control study aimed to examine consumption of folic acid supplement and high dietary folate among Nepalese women during preconception and pregnancy in association with preterm birth. A convenience sampling technique was conducted to recruit 84 mothers who delivered 42 preterm and 42 full-term babies at a hospital, Kathmandu, Nepal from March to May 2018. Research instruments included 5 self-reported questionnaires. There were a demographic questionnaire and the consumption of folic acid supplement and folate diet during preconception and pregnancy questionnaires. Information about preterm births was obtained from medical records. Descriptive statistics, t-test, chi- square test and multiple logistic regression analysis were computed for data analysis.

Results showed that during preconception and pregnancy, women who consumed more on high dietary folate were less likely to have preterm births comparing to those who consumed less (OR = .20, 95%CI = .06-.67 and OR = .53, 95%CI = .32-.92, respectively). Consumption of folic acid supplement during preconception did not associated with preterm birth. However, women who consumed more on folic acid supplement during pregnancy were less likely to have preterm birth comparing to those who consumed less (OR = .53, 95%CI = .32-.92). These findings support previous studies that having more consumption on high dietary folate during preconception and pregnancy, as well as folic acid supplement during pregnancy could reduce the risk of preterm birth.

Key words: Folic acid supplement, high dietary folate, preconception, pregnancy, preterm birth.

บทคัดย่อ

การวิจัยแบบแบบมีกลุ่มควบคุมครั้งนี้มีวัตถุประสงค์เพื่อศึกษาการรับประทานกรดโฟลิกเสริมและอาหารที่มีโฟเลทสูงในสตรีชาวเนปาลระยะก่อนตั้งครรภ์และระยะ

[1] Student of Master of Nursing Science (International Program), Faculty of Nursing, Burapha University
[2] Associate Professor, Faculty of Nursing, Burapha University
[3] Assistant Professor, Faculty of Nursing, Burapha University
* Corresponding author email: wannee@buu.ac.th

ตั้งครรภ์ที่มีความสัมพันธ์กับการคลอดก่อนกำหนด กลุ่มตัวอย่างคัดเลือกแบบสะดวกจำนวน 84 คน เป็นมารดาที่คลอดบุตรก่อนกำหนด (จำนวน 42 คน) และคลอดบุตรครบกำหนด (จำนวน 42 คน) ที่โรงพยาบาลแห่งหนึ่งในเมืองกาฐมาณฑุ ประเทศเนปาล ในระหว่างเดือนมีนาคม ถึงเดือนเมษายน พ.ศ. 2561 เครื่องมือที่ใช้ในการวิจัยเป็นแบบสอบถามจำนวน 5 ชุดที่ให้กลุ่มตัวอย่างเป็นผู้ตอบเอง ได้แก่ แบบสอบถามข้อมูลทั่วไป แบบสอบถามการรับประทานกรดโฟลิกเสริมในระยะก่อนตั้งครรภ์และระยะตั้งครรภ์ และแบบสอบถามการรับประทานอาหารที่มีโฟเลทสูงในระยะก่อนตั้งครรภ์และระยะตั้งครรภ์ ข้อมูลเกี่ยวกับการคลอดได้จากบันทึกของโรงพยาบาล วิเคราะห์ข้อมูลด้วยสถิติพรรณา การทดสอบที การทดสอบไคสแควร์ และการวิเคราะห์ถดถอยโลจิสติกแบบมัลติเปิล

ผลการวิจัยพบว่า ในระยะก่อนตั้งครรภ์และระยะตั้งครรภ์ สตรีกลุ่มตัวอย่างที่รับประทานอาหารที่มีโฟเลทสูงมากกว่า มีการคลอดก่อนกำหนดน้อยกว่าสตรีที่รับประทานอาหารที่มีโฟเลทสูงน้อยกว่า (OR = .20, 95%CI = .06-.67 และ OR = .53, 95%CI = .32-.92 ตามลำดับ) การรับประทานกรดโฟลิกเสริมมากในระยะก่อนตั้งครรภ์ไม่มีความสัมพันธ์กับการคลอดก่อนกำหนด แต่การรับประทานกรดโฟลิกเสริมมากในระยะตั้งครรภ์มีการคลอดก่อนกำหนดน้อยกว่าเมื่อเทียบกับสตรีที่รับประทานกรดโฟลิกเสริมน้อย (OR = .53, 95%CI = .32-.92) ผลการวิจัยครั้งนี้สนับสนุนผลการวิจัยที่ผ่านมาว่าการรับประทานสารอาหารที่มีโฟเลทสูงในระยะก่อนตั้งครรภ์และระยะตั้งครรภ์ รวมทั้งการรับประทานกรดโฟลิกเสริมในระยะตั้งครรภ์ สามารถลดความเสี่ยงต่อการคลอดก่อนกำหนดได้

คำสำคัญ: กรดโฟลิกเสริม สารอาหารที่มีโฟเลทสูง ระยะก่อนตั้งครรภ์ ระยะตั้งครรภ์ การคลอดก่อนกำหนด

Significance of the problem

Preterm birth is coming up as the second leading cause of death among children under five years of age (Sharif, Mohamedain, Ahmed, Nasr, & Adam, 2017). It is estimated that approximately 15 million babies were born preterm worldwide (World health Organization [WHO], 2018). The rate of preterm birth is more alarming in Southeast Asia, as Bangladesh (19.8%), India (27.5%), Indonesia (18.9%), and Pakistan (23.6%) (Liu et al., 2015). Despite of having universal access to health care utilization and high quality of prenatal care in high-income countries, every year 6 to 1000 newborn babies die during their first year of life mainly due to preterm birth, birth defects and maternal complication during pregnancy (WHO, 2012). Child mortality in sub-Saharan Africa and South Asia is 29 times greater than those in industrialized countries (175 deaths per 1,000 live births). In 2016, child mortality rate in Nepal was 34.5 deaths per 1,000 live births. Preterm birth causes 29% neonatal death and 14% under five death globally and influencing many health problems such as learning disabilities, auditory, visual impairment in later stage of life (Liu et al., 2015).

Although the actual cause of preterm birth is still idiopathic but there are many factors which cause preterm birth such as obstetric, medical and nutrition. Among many nutrient factors, inadequate folate found to have association with adverse pregnancy outcomes, such as neural tube defects, fetal growth restriction and preterm delivery (Sengpiel et al., 2013). Folate is one of the major components of nutrition and water-soluble vitamin B9, which has an important role in DNA synthesis, repair, methylation and rapid and division of cell (Zheng et al., 2016). Consumption of adequate amount of dietary folate during preconception and first trimester of pregnancy found to have association with preterm birth (Liu et al., 2016). This essential nutrient can be consumed from various diets such as dark green vegetables, grains, beans and peas, fruits and organ meats and folic acid supplement, which can

be taken as a tablet (Health Canada, 2008; Zheng et al., 2016). It is found that daily consumption of 5mg of folic acid supplement during early and mid-pregnancy could reduce about 8% of chance of prematurity (Zheng et al., 2016). Therefore, folate has been investigated substantially as a protective factor for preterm birth because of its increased demand during pregnancy and it is proven potencial in preventing neural tube defects and preterm birth in babies (Liu et al., 2016).

Nepal is a low-income country in South Asia, and has a high rate of preterm birth. It is about 14% per 1000 live birth and 4,300 under five years children die due to direct complication of preterm birth (Kc et al., 2015). The general health status of the reproductive aged women in Nepal is poor, hypertension, jaundice, and anemia. Anemia is quite high among pregnant women (Bhandari, Sayami, Sayami, Kandel, & Banjara, 2014). Though, the Nepali government has implemented a number of nutritional strategies to reduce the rate of maternal mortality and morbidity. The consumption rate of folic acid supplement was increased during pregnancy. However, the majority of women (79%) were still unaware about the concept of preconception care and importance of consuming diet rich in folate (Bhandari, Sayami, Sayami, Kandel, & Banjara, 2014; Nisar Dibley, & Aguayo, 2016). It was found insufficient knowledge and practice regarding the consumption and regular intake of folic acid and folate during preconception among Nepali women (Gautam, & Dhakal, 2016; Paudel, Wing, & Silpakar, 2012).There are several studies conducted in Nepal related to folic acid supplement, nutritional status in pregnancy, anemia, and preterm birth. However, no study has been found to investigate the association of consumption of folic acid and dietary folate during preconception and pregnancy with preterm birth among postnatal mothers in Nepal.

By determining the association of neonatal death in babies born prematurely and low and inadequate consumption of folic acid supplement and dietary folate in preconception and during pregnancy, the findings from this study would provide the need for conduct low-economic educational campaign for women and family about the importance of consumption of folic acid and dietary folate during preconception and pregnancy. Therefore, it is important to examine the influencing of consumption of folic acid supplement and dietary folate on preterm birth in preconception and during pregnancy among Nepali women.

Objective of the study

To determine the influencing of consumption of folic acid supplement and dietary folate in preconception and during pregnancy on preterm birth among Nepalese postnatal women.

Conceptual framework

The conceptual framework of this study is synthesized from the empirical literature on evidence of consumption of folic acid supplement and dietary folate in preconception and throughout the pregnancy and its association with preterm birth. Folate is the vitamin that is consumed from the different type of diet whereas folic acid is the supplement and is a synthetic form of folate. Both are taken to overcome the lack of vitamin B9 and minerals in the body. Right dose of consuming folic acid is not only preventing the deficiency of this essential micronutrient but also helps to have better pregnancy outcomes. It helps in

development of the baby from intrauterine life (WHO, 2012). WHO (2012) recommends having 30 - 60 mg of daily intake of folic acid for preconception period and throughout pregnancy could prevent birth complications and adverse birth outcomes. It is found that consuming diet containing folate and folic acid supplement in preconception and first trimester of pregnancy are more helpful to prevent babies from preterm birth (Kc et al., 2015; Zheng et al., 2016). The conceptual framework of this study is presented in figure 1.

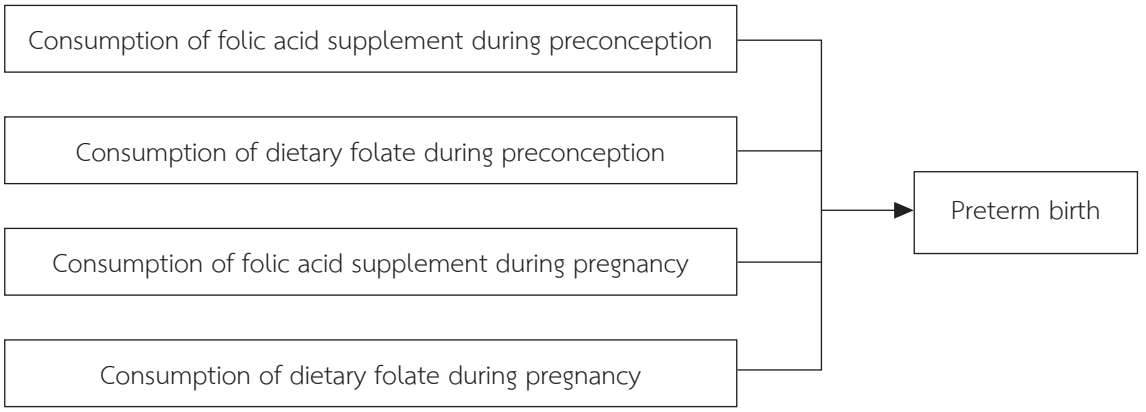

Figure 1 Conceptual framework of the study

Methods

A case-control design was conducted in postpartum ward of Paropakar Maternity and Women's Hospital, Kathmandu, Nepal.The study was conducted from March to May 2018.

Target population was women who delivered preterm birth and the women who delivered the fullterm birth at postpartum ward of the Paropakar Maternity and Women's Hospital, Kathmandu, Nepal.

Sample: A convenience sampling technique was used to recruit participants from the target population. The inclusion criteria for these participants were: 1) Age ≥ 18 years, 2) Nepali national, 3) Singleton delivery, 4) who can read and write Nepalese language, 5) Women having no leading disease that cause preterm birth.

A sample size was calculated by using Tabachnick and Fidell (2007) as follows: n = 50 + 8m (where n is sample size, m is the number of independent variables). This study has 4 independent variables. Therefore, the sample size should be at least 80 participants. In this study, there were 84 participants. Since this study design has 1:1 ratio, so 84/2 = 42 as a case group (mother delivered preterm birth) and 42 as control group (mother delivered full term birth) were obtained.

Research Instruments

Data were collected using 5 self-reported questionnaires.

A demographic questionnaire: It is divided into demographic and obstetric history of the participants.

Consumptions of folic acid supplement in preconception (CFASP) questionnaire was developed by the researcher based on reviewing related literature (Alfenso, von Ehrenstein,

Bandoli, & Ritz, 2016; Zheng et al., 2016). It was used to collect the information of consumption of folic acid supplement by women one month before conception. Answers of two items classified women into 2 categories that was, 0= not using folic acid supplement at all during preconception, and 1= women consumed folic acid supplement during preconception. Question no. 2 has two categories among women that was "everyday use" considered that women taking folic acid supplement as per recommendation of World Health Organization and "sometime" users were evaluated as a non-user.

Consumptions of folic acid supplements during pregnancy (CFASDP) questionnaire was developed by the researcher based on reviewing related literature (Alfenso et al., 2016; Zheng et al., 2016). There are 3 questions were to obtained information about the portion and frequency of consumption of folic acid supplements by women in whole three trimester of pregnancy. The total score ranges from 3 items was 0-9. A higher score indicates to be the users of folic acid supplement according to recommendation of World Health Organization.

Consumption of dietary folate in preconception (CDFP) questionnaire was developed by the researcher based on reviewing related literature (Health Canada, 2008). It was used to collect information about portion and frequency of consumption of dietary folate in preconception. The total score ranges from 7 items was 0-28. A higher score indicates high consumption of dietary folate in preconception.

Consumption of dietary folate during pregnancy (CDFDP) questionnaire was developed by the researcher based on reviewing related literature. This section was about to obtain the information of women's dietary habit and consumption of dietary folate during pregnancy. The total score ranged from 7 items was 0-28. A higher score indicates high consumption of dietary folate during pregnancy.

Test of psychometric properties of the research instruments

Content validity: Five experts were selected from the area of nursing research, midwifery, obstetrics and gynecology for the content validity of the newly developed questionnaires. Questionnaires were developed in English, and later were back translated into Nepali language as recommended by Cha, Kim, and Erlen, (2007).

Reliability: In this study, three questionnaires were tested for internal consistency among 20 women who had similar characteristics to the study sample in Paropakar maternity and women's hospital. Cronbach's alpha coefficients obtained for dietary folate consumption in preconception was .81, consumption of dietary folate during pregnancy was .76 and for folic acid supplement during pregnancy was .83.

Ethical consideration

The research was approved by the Institutional Review Board [IRB] for Graduates Studies (approval no. 02-02-2561), Faculty of Nursing, Burapha University, Thailand. Further, it was reviewed and approved by the National Health Research Council (NHRC) and Research Ethical Board of Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu, Nepal.

Data collection procedures

The participants were recruited solely on a voluntary basis. The consent from the participant was obtained prior to the data collection. The researcher collected data from 9:00 am to 4.00

pm for those who met the inclusion criteria. It took 15-20 minutes to complete the questionnaire.

Data analysis

Data were coded and entered into a statistical software program for analysis. The significance level was set as $p < .05$. Descriptive statistics were used to describe the demographic information. Binary logistic regression was used to examine the influencing factors of preterm birth.

Results

There were 84 women participating in this study comprising equal number of preterm and full-term births. No statistical difference was found between demographic characteristics between the case and the control groups. A mean age of women with preterm birth was 21.4 years (SD = .65) while a mean age of women with full-term birth was 25.1 years (SD = .17). For both groups of participants, gravida and parity was about 1. More than one half completed secondary school, were married, housewife, never had miscarriage, and no history of preterm birth or abortion. Most of them were also not smoking.

Participants who had more consumption of folic acid supplement during preconception and pregnancy had significant relationship with preterm birth. Similarly, participants who had more consumption on folic acid supplement (p-<.01) and high dietary folate during pregnancy were also found to have significant association with preterm birth (Table 1).

Table 1 Association of consumption of folic acid and dietary folate with preterm birth

Variables	Preterm (n=42)		Full term (n=42)		*p*-value
	n	%	n	%	
Folic acid supplement during preconception					
Not used	42	56	33	44	.00[c]
Used	0	0	9	100	
	M (SD)		M (SD)		
High dietary folate during preconception	20.26 (2.97)		24.60 (1.78)		.00a
High dietary folate during pregnancy	21.10 (2.66)		23.88 (1.23)		<.01a
Folic acid supplement during pregnancy	0.59 (0.91)		6.45 (1.15)		.00a

[a] *t*-test, [c] Fisher exact test

Multiple logistic regression analysis was performed to examine predictors of preterm birth among women who delivered preterm and full-term births using significant factors from the univariate analysis including consumption of folic acid supplement during preconception and pregnancy, consumption of high dietary folate in preconception and during pregnancy. In table 2, the Omnibus test model coefficients indicated that p-value of this model was less than .05. The odds of having preterm birth was 40% (OR: .60, 95% CI: .42- .88) in women who consume enough high dietary folate during preconception. In addition, the odds of having preterm birth is 80%

(OR: .20, 95% CI: .06-.67) and 47% (OR: .53, 95% CI: .32-92) in women who had adequate consumption of folic acid supplement during pregnancy and high dietary folate during pregnancy, respectively.

Table 2 Factors predicting preterm birth

Predictors	B	S.E.	Wald	*p*	OR	95%CI
FAS during PC	18.573	11327.7	0.00	.99	0.00	0
High dietary folate during PC	-0.504	0.19	7.01	.08	0.60	0.42-0.88
FAS during pregnancy	-1.590	0.60	6.94	.08	0.20	0.06-0.67
High dietary folate during pregnancy	-0.633	0.28	5.14	.02	0.53	0.32-0.92

FAS= folic acid supplement, PC= preconception

Discussion

The findings of this study showed only three significant predictors which were consumption of folic acid during pregnancy, consumption of dietary folate before and during pregnancy. Results of logistic regression showed that women who have more consumption of high dietary folate such as dark green vegetables, whole grains, meats and fruits during preconception was .06 times less likely to have preterm birth (OR = 0.60, 95% CI = 0.42-0.88) compared to women who consume less amount of high dietary folate. A similar study carried out in Australia showed consuming high folate diet in preconception and associated with preterm birth (OR: .31, 95% CI: .31-.73) (Griger, Grzeskowaik, & Clifton, 2014). This is consistent with another cohort study conducted in China. They found that intake of high dietary folate during preconception could reduce the risk of preterm birth by .68 times (OR: 0.68, 95% CI: 0.56-0.83) (Liu et al., 2016). This finding suggested that women should have sufficient knowledge about the importance of nutrition and utilization of diet which contains high folate before getting pregnant to minimize the risk of preterm birth.

The finding of the study showed odds of having preterm birth among women who had high consumption of folic acid supplement continuously throughout the pregnancy which was 0.20 times less likely to have preterm birth (OR = .20 95% CI = 0.06-0.67) comparing to those who did not consume folic acid supplement regularly during pregnancy. This finding is consistent with many studies which showed a slight reduction of preterm birth among women receiving folic acid supplement during pregnancy (Mantovani, Filippini, Bortolus, & Franchi, 2014). In addition, finding from China also showed that consuming folic acid supplement in early trimester of pregnancy was .61 times less likely to have preterm birth (OR .61 95% CI = 0.58, 0.65) (OR 0.61 95% CI = 0.58, 0.65) (Liu et al. 2016). Results of previous studies and this study support a possible protective effect of folic acid supplement on preterm birth.

The results also found that women who consumed high dietary folate during pregnancy were 0.53 times less likely to have preterm birth (OR = 0.53, 95% CI = 0.32-0.92) than women who had less consumption of dietary folate during

pregnancy. Similar study conducted in China showed that consuming adequate dietary folate during pregnancy can reduce .68 times (OR = 0.61, 95% CI = 0.43-0.87) the risk of preterm birth (Liu et al., 2016).

Consumption of folic acid supplement during preconception was not found as a predictor to preterm birth which is inconsistent with a study from China which indicated that daily intake of 400 µg folic acid alone during the periconceptional period was associated with reduction the risk of spontaneous preterm birth (Li, Ye, Zhang, Li, Liu, & Ren, 2014). However, this study is consistent with a study in Sweden which found that there was no significant association with preterm birth when folic acid supplement was initiated within 8 weeks preconception (Sengpiel et al., 2013).

Implication for nursing

To promote the healthy outcome of pregnancy and reduce the risk of preterm birth, nurses and midwives can emphasize on intervention and starts educational campaign that can put light on importance of consuming folic acid supplements and folate diet regularly.

Future research should include more types of food that contain high folate, which is locally available in different parts of the country. A larger sample size can give good concept for promoting dietary folate from grassroot level. The findings of the study regarding folic acid supplement during pregnancy strongly advocates the need for free supply of folic acid supplement by government from beginning of the first trimester of pregnancy.

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