Effects of maternal folic acid supplementation on renal urinary system development in human offspring—a meta-analysis and systemic review

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Background: The effectiveness of maternal folate acid (FA) supplementation during pregnancy in reducing the risk of neural tube defects (NTDs) is already well established. However, the effect of maternal FA supplementation on congenital anomalies of the kidney and urinary tract (CAKUT) has scarcely been investigated. This study aimed to investigate the evidence of associations between maternal FA supplementation and offspring renal urinary system abnormality outcomes.

Methods: The PubMed, Web of Science, CINAHL, Cochrane, EMBASE, MEDLINE, and Scopus databases were searched. The meta-analysis used a random effects model to obtain the total odds ratio (OR) for each outcome through Review Manager (5.4.1). This study protocol was registered in PROSPERO with protocol number (CRD42023397185).

Results: Eight studies were included. For the meta-analysis, 48,796,782 participants were included in the maternal FA-supplemented group and 58,394,898 participants were included in the maternal FA-unsupplemented group. Maternal FA supplementation was discovered to be possibly relevant to an increased risk of CAKUT (OR =1.14, 95% CI, 1.02 to 1.27) (P=0.02). Subgroup analysis of patients with different types of CAKUT showed significantly increased cystic kidney incidence (OR =1.66, 95% CI, 1.26 to 2.19) (P=0.0004).

Conclusions: Despite the limitations, maternal FA supplementation might be relevant to offspring CAKUT, especially cystic kidney. Prescription of FA supplementation for pregnant women might carefully censored, especially for pregnant mothers with a family history of kidney disease. However, the dose-dependent effect on CAKUT remains unclear and needs further research.

Keywords: Maternal folate acid supplementation; congenital anomalies of the kidney and urinary tract (CAKUT); cystic kidney; meta-analysis

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) refer to a group of malformations. The international occurrence of CAKUT is as high as 6/1,000, accounting for 30–50% of all prenatal diagnostic malformations, which is the main reason for end-stage kidney disease in children (1).

By constructing a variety of knockout animal models,

such as zebrafish, toad, and mice models, and screening human pathogenic genes, most scholars currently believe that gene mutations and environmental factors are the two main factors of CAKUT pathogenesis (2). In recent years, adverse environmental factors during pregnancy have gradually attracted the attention of researchers, who believe that adverse intrauterine environmental factors also play an essential role in the pathogenesis of CAKUT. On the one hand, large population retrospective studies discovered some adverse intrauterine factors correlated with CAKUT, such as a low-protein diet, gestational diabetes, drinking, smoking, and folate deficiency. On the other hand, by constructing mouse models of a low-protein diet during pregnancy, intrauterine hypoxia, and gestational diabetes mellitus to simulate the adverse factors of intrauterine growth retardation (IUGR) (3), hypoxia (4), and high sugar (5), it was confirmed that the above factors could increase the incidence of CAKUT in mice.

A recent study (6) compared the differences in intrauterine environmental factors in 562 patients with CAKUT and 2,139 normal control participants and proposed that *in vitro* fertilization and gestational diabetes may be relevant to the occurrence of CAKUT, while maternal usage of folic acid (FA) increases the risk of CAKUT. The Canfield MA (7) and Godwin KA (8) studies also suggested that FA use is associated with CAKUT. Moreover, some studies (9) have found that the use of

FA during pregnancy does not adversely affect children or cause renal urinary system malformations but indeed has a protective effect against neural tube developmental malformations. In summary, the current research on the effect of FA supplementation on the development of the renal urinary system is controversial, and there is a lack of reports on relevant animal models.

Therefore, a meta-analysis review and analysis of the relevance of maternal FA supplementation and renal urinary system structural abnormalities in human offspring was proposed. We present this article in accordance with the PRISMA reporting checklist (available at https://pm.amegroups.com/article/view/10.21037/pm-23-11/rc) (10).

Methods

This systematic review protocol was registered with the online Prospero database (CRD42023397185) (11).

Search strategy

We searched the PubMed, Web of Science, CINAHL, Cochrane, EMBASE, MEDLINE, and Scopus databases. The search terms included three groups: (I) pregnancy or pregnant* or lateral or prenatal or maternal or mother*; (II) folate or felsite or folacin or "folic acid, *" or "vitamin B9" or "vitamin M, *" or "B9, vitamin" or "pteroylglutamic acid"; and (III) kidney or nephron* or renal or urinary or uret*.

Inclusion criteria

Types of participants
This meta-analysis review only included human research, and all female participants had to be pregnant (at any stage of gestation or in the periconceptional period) and successfully deliver the baby during the time of the study.

Types of studies
This meta-analysis review involved experimental studies, including pre–post studies, pseudo-randomized controlled trials (RCTs), and experimental RCTs, and observational studies, including case-control studies, cross-sectional studies, and prospective and retrospective cohort studies.

Types of interventions
The intervention in this meta-analysis was maternal FA supplementation during pregnancy (at any stage of gestation

Highlight box

Key findings
- Maternal folic acid (FA) supplementation might be relevant to offspring congenital anomalies of the kidney and urinary tract (CAKUT), especially cystic kidney.

What is known and what is new?
- Previous studies had found that the use of FA during pregnancy indeed has a protective effect against neural tube developmental malformation.
- Maternal FA supplementation may be associated with offspring CAKUT, especially cystic kidney.

What is the implication, and what should change now?
- Prescription of FA supplementation for pregnant women should be carefully censored, especially for pregnant mothers with a family history of kidney disease. The precise-timing and individuated-dose for FA supplementation during pregnancy remains unclear and needs further research.
- The overall limited quality of relevant case-control studies necessitates further high-quality researches.

or in the periconceptional period).

Types of outcome measures

Studies that included a measure of offspring kidney structure as a primary or secondary outcome were considered for inclusion.

Study selection

All identified articles were retrieved and exported to EndNote and screened following four steps: (I) titles, abstracts, descriptions, and MeSH headings were used to assess study inclusion; (II) full texts for the literature that satisfied the inclusion criteria from step 1 were retrieved; (III) the final full papers were retrieved for review and data extraction; and (IV) all steps were completed independently by two reviewers, and when there was disagreement at any step, a final decision was independently made by a third reviewer.

Study quality

All included studies were assessed for methodological quality using the American Dietetic Association Quality Criteria Checklist (12), and the overall quality of the final studies was rated as positive, neutral, or negative by two independent reviewers, while a third reviewer was consulted when needed. No studies were excluded based on quality ratings.

Data extraction and synthesis

One reviewer carried out data extraction and was cross-checked by a second reviewer independently, including data on the study design, intervention characteristics, participant information, and data related to review outcomes. Meta-analysis of data was not expected due to folate deficiency in pregnant women, heterogeneity in folate supplementation, and measures of renal urinary system outcomes. Thus, the influence of maternal FA supplementation on offspring renal urinary system structure is described in a narrative review.

Statistical analysis

The meta-analysis used a random effects model to obtain the total odds ratio (OR) for each outcome through Review Manager (5.4.1). All statistical analyses were performed using STATA. Unless otherwise stated, $P<0.05$ was considered statistically significant.

Results

Study selection

The initial literature screening identified 1,806 articles after removing duplicate papers (*Figure 1*), and 1,773 articles were excluded following the title and abstract review. Despite online interlibrary searches, the full texts of 3 studies were unavailable, and 14 studies were not published in English. Ultimately, 16 full-text papers were retrieved. The reasons for the removal of full-text articles were as follows: the outcomes were not related to offspring renal outcomes (n=2); detailed clinical kidney outcomes were not reported (n=3); and the supplements were multivitamins for which no detailed information on FA dosage was available (n=3). The remaining 8 articles were included in this current meta-analysis and focused on maternal FA supplementation and offspring renal urinary system outcomes.

Study characteristics

The 8 included articles were published from 1998 to 2020. In the included literature (*Table 1*), RCTs (n=1), controlled cohort trials (n=1), case-control studies (n=3), a prospective study (n=1) and descriptive studies (n=2) illustrated the association between maternal FA supplementation and offspring kidney malformations. Only 3 articles did not have the detailed dose of FA supplementation during pregnancy: the study by Groen In 't Woud *et al.* (6) used only the questionnaire method to determine whether the pregnant mothers used folic acid products during pregnancy, and the dose was not described in detail; the study by Canfield (7) and Botto (17) was performed after the implementation of the FA-fortification policy, and the trend of renal development malformations in offspring before and after the FA-fortification intervention were compared; and the study by Botto evaluated the specific strengthening policy (17).

Maternal FA supplementation and renal urinary system defects

In this study, 8 original articles were included to explore the association between maternal FA supplementation and offspring renal urinary system development malformations, and a total of 48,796,782 participants were included in the
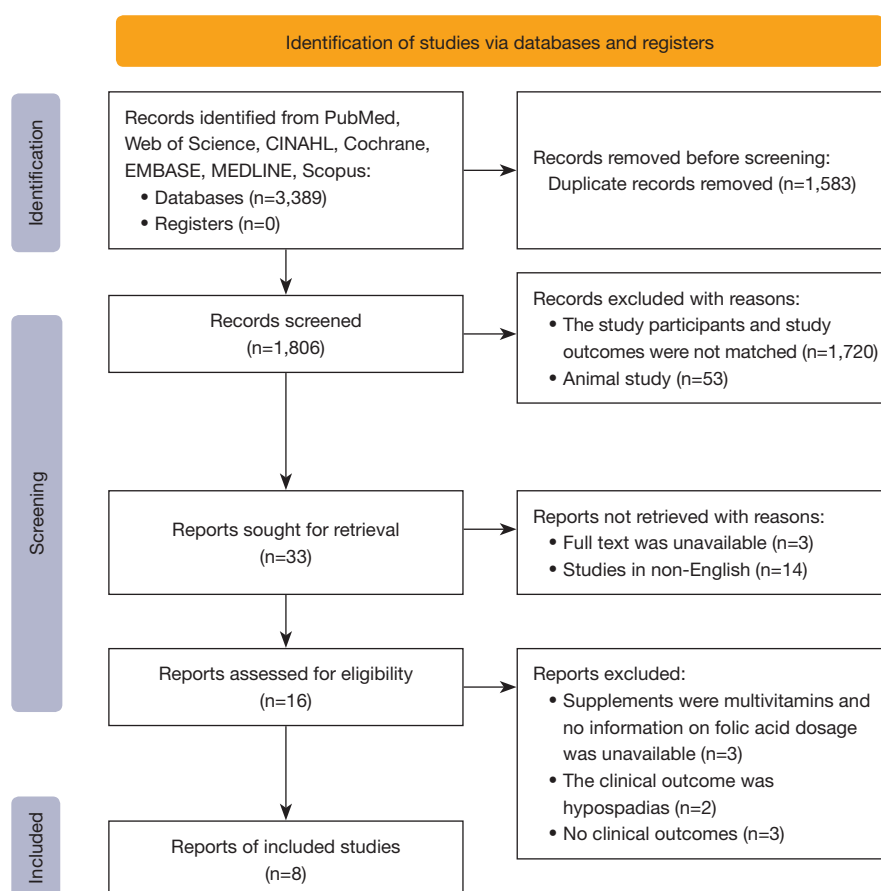
Figure 1 Flow diagram of publications screening.

FA-supplemented group and 58,394,898 participants were included in the FA-unsupplemented group. The forest plot (*Figure 2*) shows that maternal FA supplementation was related to an increased risk of offspring CAKUT (OR =1.14; 95% CI, 1.02–1.27; P=0.02). However, there was significant heterogeneity in the results of all studies (I^2=88%).

CAKUT clinical phenotypes are abundant, and different environmental factors may inconsistently increase the risk of CAKUT with special phenotypes. Thus, subgroup analysis of patients with different types of CAKUT, including hydronephrosis, renal a/dysgenesis, and cystic kidney, was performed in this study. The results (*Figure 3*) demonstrated that maternal FA supplementation contributed to a significantly increased risk of offspring cystic kidney (OR =1.66; 95% CI, 1.26–2.19; P=0.0004). However, the risk of offspring hydronephrosis (OR =0.95; 95% CI, 0.71–1.29; P=0.76) and the effect of renal a/dysgenesis (OR =0.94; 95% CI, 0.73–1.21; P=0.64) showed non-statistical significance. At the same time, after CAKUT grouping, the

heterogeneity of each group was still high (I^2=81.1%).

Different doses of FA supplementation can be related to the incidence of CAKUT, so this study additionally defined the FA supplementation dose in the subgroup analysis, including five studies with exact FA supplementation measurements, and grouped participants based on FA supplementation (doses of 0.2 mg per day, 0.4 mg per day, and 0.6 mg per day). Heterogeneity was appreciably decreased among the subgroups (I^2=0) (*Figure 4*). When FA supplementation was ≤0.2 mg/day for the duration of pregnancy, the CAKUT incidence in offspring was decreased (OR =0.95; 95% CI, 0.61–1.48; P=0.81). When FA supplementation was >0.2 mg/day during pregnancy, the incidence of CAKUT increased in offspring (OR =1.08; 95% CI, 0.86–1.36; P=0.50). When FA supplementation was ≤0.4 mg/day during pregnancy, the prevalence of CAKUT increased (OR =1.04; 95% CI, 0.81–1.34), even though there was no statistically significant difference (P=0.74). When maternal FA supplementation was >0.4 mg/day

Table 1 Characteristics and effect values of the included study

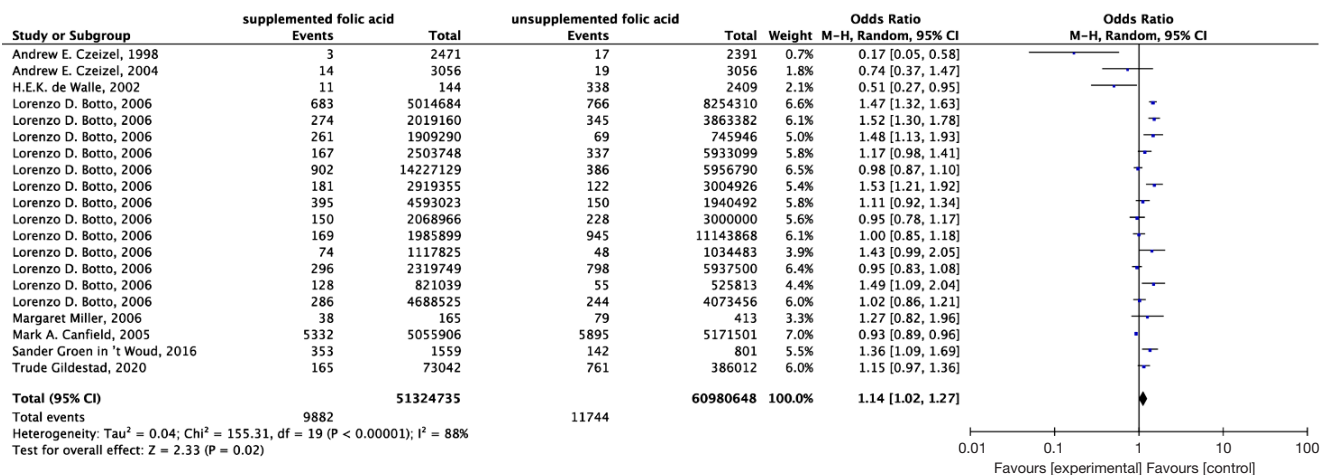| References	Setting	Aims	Design	Sample size	Years	Details of intervention	Data acquisition
Gildestad 2020 (13)	Medical Birth Registry of Norway (MBRN)	Compared the risks of organ-specific major birth defects in live- and stillborn infants of mothers who did or did not use folic acid and/or multivitamin supplements	Prospective study	894,927 live and stillborn infants	1999 to 2013	Folic acid tablets available over the counter in Norway during the study period contained 0.4 mg of folic acid. The maximum limit of folic acid in multivitamins was 0.2 mg	Information on supplement use is collected during pregnancy and transferred to the birth notification form
Groen In 't Woud 2016 (6)	AGORA (Aetiologic research into Genetic and Occupational/ environmental Risk factors for Anomalies in children) data- and biobank	Studied potential maternal risk factors in individual phenotypes within the congenital anomalies of the kidney and urinary tract (CAKUT) spectrum	Case-control study	562 children with CAKUT; 2,139 healthy controls	January 1990 to March 2011	Mothers were considered to have used folic acid when they reported use of folic acid supplements only, folic acid-containing multivitamins, or a combination of folic acid and multivitamin supplements from 1 month before conception through the eighth week after conception	Questionnaire data
Bower 2006 (9)	Non-neural birth defects in Western Australia	Investigate whether maternal periconceptional folate intake is associated with a reduction in selected non-neural birth defects in Western Australia	Case-control study	Case 522; Control 578	January 1997 to December 1999	Women consuming an average of 0.2 mg or more daily from supplements for each of four time periods the month before pregnancy and each of the first three months of pregnancy were considered to be adequately supplemented and were compared with women taking less than 0.2 mg a day	All eligible case and control women were invited by mail to complete a pregnancy/demographic questionnaire and a semiquantitative food frequency dietary questionnaire
Canfield 2005 (7)	National Birth Defects Prevention Network (NBDPN)	Examined whether folic acid fortification might have decreased the prevalence of other specific birth defects	Descriptive study	Using population-based data from 23 state member programs of the NBDPN	1995 to 2000	Optional fortification of the grain supply was initiated as early as late 1996, by law, fortification of all enriched grain products was to be completed by January 1, 1998	Focused on two delivery time periods, 1995–1996 and 1999–2000
Czeizel 2004 (14)	Hungarian Periconceptional Service	The 1984–1991 Hungarian randomized controlled trial of periconceptional multivitamin supplementation (PMVS) containing folic acid showed a significant reduction in the first occurrence of neural tube defects, and of urinary tract and cardiovascular abnormalities, but no reduction in orofacial clefts. A controlled cohort trial was designed to confirm or deny these results	Controlled cohort trial	Supplemented cohort 3,056; Unsupplemented cohort 3,056	May 1993 to April 1996	Supplemented women were recruited from the HPS using the same multivitamin as the Hungarian randomized controlled trials (RCTs). PMVS containing 0.8 mg folic acid. Unsupplemented pregnant women were recruited in the standard regional antenatal care clinics and were matched to each supplemented pregnant woman on the basis of age, socioeconomic status, place of residence, and year of pregnancy	Both supplemented and unsupplemented cohort women were asked to bring their completed pregnancy outcome certificate personally or send it by mail to the appropriate center of the HPS or cohort-controlled trial after the completion of their pregnancy
De Walle 2003 (15)	European Surveillance of Congenital Anomalies (EUROCAT) northern Netherlands registry	Investigated the possible preventive effect of folic acid in five selected groups of malformations	Case-control study	267,937 live and stillborn infants; 2,751 cases were defined as infants with folic acid (FA) sensitive defects; 3,647 controls were all children and fetuses with anomalies other than the sensitive anomalies	1981 to 1998	Folic acid intake was defined as intake of 0.4 mg of folic acid daily starting before conception until 8 weeks after conception. If mothers took some folic acid but not during the entire period the infants were excluded from the analyses	Information on FA use was collected via the physician, pharmacist and mother
Czeizel 1998 (16)	Hungarian Periconceptional Service (HPS)	A summary about the final results of the Hungarian double-blind placebo controlled randomized trial of periconceptional folic acid containing multivitamin and trace element supplementation	Randomized clinical trials	3,953 multivitamins; 3,952 trace element	1984 to 1991	Supplemented women were recruited from the HPS using the same multivitamin as the Hungarian RCT. The Hungarian double-blind randomized trial of PMVS (0.8 mg) and placebo like trace element supplementation was part of the periconceptional care	Women were asked to bring their completed pregnancy outcome certificate personally or send it by mail to the appropriate center of the HPS
Botto 2006 (17)	15 registries that are members of the International Clearinghouse for Birth Defects Monitoring Systems (recently renamed International Clearinghouse for Birth Defects Surveillance and Research)	Whether supplementation recommendations alone, without fortification, are effective in reducing the population-wide rates of neural tube defects, and whether such policies can reduce the occurrence of other birth defects	Descriptive study	1.5 million births yearly (1,000,000 from Europe, 370,000 from Canada and the United States, and 87,000 from Australia)	1980 to 2003	Recommend the use of daily supplements 1 from before conception varied by countries, regions	Gathered information on folic acid policies from interviews of the Program Director of the registry, publications listed on MEDLINE, reports of workshops and committees, and documents issued by governmental agencies and professional bodies

Study or Subgroup	supplemented folic acid Events	Total	unsupplemented folic acid Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Andrew E. Czeizel, 1998	3	2471	17	2391	0.7%	0.17 [0.05, 0.58]	
Andrew E. Czeizel, 2004	14	3056	19	3056	1.8%	0.74 [0.37, 1.47]	
H.E.K. de Walle, 2002	11	144	338	2409	2.1%	0.51 [0.27, 0.95]	
Lorenzo D. Botto, 2006	683	5014684	766	8254310	6.6%	1.47 [1.32, 1.63]	
Lorenzo D. Botto, 2006	274	2019160	345	3863382	6.1%	1.52 [1.30, 1.78]	
Lorenzo D. Botto, 2006	261	1909290	69	745946	5.0%	1.48 [1.13, 1.93]	
Lorenzo D. Botto, 2006	167	2503748	337	5933099	5.8%	1.17 [0.98, 1.41]	
Lorenzo D. Botto, 2006	902	14227129	386	5956790	6.5%	0.98 [0.87, 1.10]	
Lorenzo D. Botto, 2006	181	2919355	122	3004926	5.4%	1.53 [1.21, 1.92]	
Lorenzo D. Botto, 2006	395	4593023	150	1940492	5.8%	1.11 [0.92, 1.34]	
Lorenzo D. Botto, 2006	150	2068966	228	3000000	5.6%	0.95 [0.78, 1.17]	
Lorenzo D. Botto, 2006	169	1985899	945	11143868	6.1%	1.00 [0.85, 1.18]	
Lorenzo D. Botto, 2006	74	1117825	48	1034483	3.9%	1.43 [0.99, 2.05]	
Lorenzo D. Botto, 2006	296	2319749	798	5937500	6.4%	0.95 [0.83, 1.08]	
Lorenzo D. Botto, 2006	128	821039	55	525813	4.4%	1.49 [1.09, 2.04]	
Lorenzo D. Botto, 2006	286	4688525	244	4073456	6.0%	1.02 [0.86, 1.21]	
Margaret Miller, 2006	38	165	79	413	3.3%	1.27 [0.82, 1.96]	
Mark A. Canfield, 2005	5332	5055906	5895	5171501	7.0%	0.93 [0.89, 0.96]	
Sander Groen in 't Woud, 2016	353	1559	142	801	5.5%	1.36 [1.09, 1.69]	
Trude Gildestad, 2020	165	73042	761	386012	6.0%	1.15 [0.97, 1.36]	
Total (95% CI)		**51324735**		**60980648**	**100.0%**	**1.14 [1.02, 1.27]**	
Total events	9882		11744				

Heterogeneity: Tau² = 0.04; Chi² = 155.31, df = 19 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.33 (P = 0.02)

Figure 2 Forest plot with pooled odds ratios of the effect of supplemented folic acid on offspring CAKUT. M-H, Mantel-Haenszel; CI, confidence interval; CAKUT, congenital anomalies of the kidney and urinary tract.
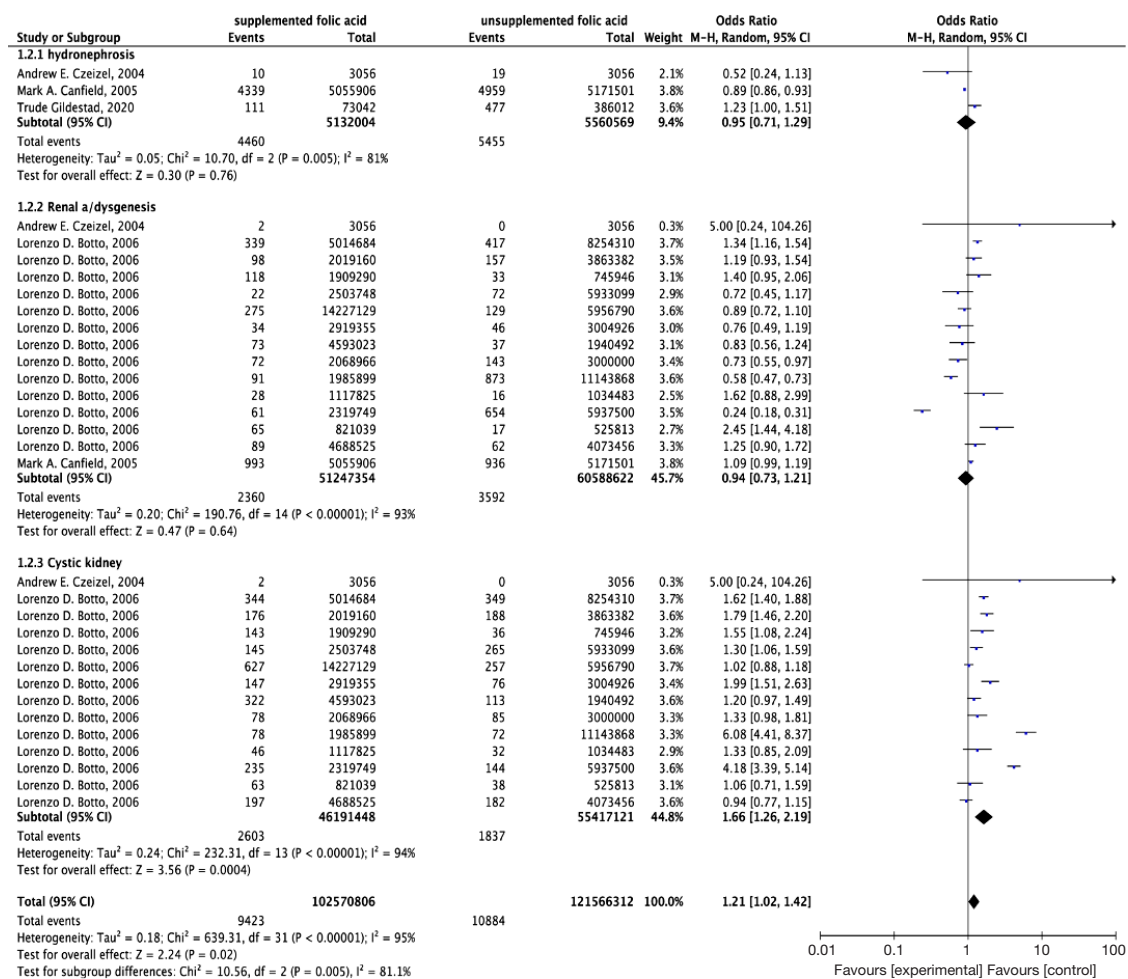
Study or Subgroup	supplemented folic acid Events	Total	unsupplemented folic acid Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
1.2.1 hydronephrosis							
Andrew E. Czeizel, 2004	10	3056	19	3056	2.1%	0.52 [0.24, 1.13]	
Mark A. Canfield, 2005	4339	5055906	4959	5171501	3.8%	0.89 [0.86, 0.93]	
Trude Gildestad, 2020	111	73042	477	386012	3.6%	1.23 [1.00, 1.51]	
Subtotal (95% CI)		5132004		5560569	9.4%	0.95 [0.71, 1.29]	
Total events	4460		5455				
Heterogeneity: Tau² = 0.05; Chi² = 10.70, df = 2 (P = 0.005); I² = 81%							
Test for overall effect: Z = 0.30 (P = 0.76)							
1.2.2 Renal a/dysgenesis							
Andrew E. Czeizel, 2004	2	3056	0	3056	0.3%	5.00 [0.24, 104.26]	
Lorenzo D. Botto, 2006	339	5014684	417	8254310	3.7%	1.34 [1.16, 1.54]	
Lorenzo D. Botto, 2006	98	2019160	157	3863382	3.5%	1.19 [0.93, 1.54]	
Lorenzo D. Botto, 2006	118	1909290	33	745946	3.1%	1.40 [0.95, 2.06]	
Lorenzo D. Botto, 2006	22	2503748	72	5933099	2.9%	0.72 [0.45, 1.17]	
Lorenzo D. Botto, 2006	275	14227129	129	5956790	3.6%	0.89 [0.72, 1.10]	
Lorenzo D. Botto, 2006	34	2919355	46	3004926	3.0%	0.76 [0.49, 1.19]	
Lorenzo D. Botto, 2006	73	4593023	37	1940492	3.1%	0.83 [0.56, 1.24]	
Lorenzo D. Botto, 2006	72	2068966	143	3000000	3.4%	0.73 [0.55, 0.97]	
Lorenzo D. Botto, 2006	91	1985899	873	11143868	3.6%	0.58 [0.47, 0.73]	
Lorenzo D. Botto, 2006	28	1117825	16	1034483	2.5%	1.62 [0.88, 2.99]	
Lorenzo D. Botto, 2006	61	2319749	654	5937500	3.5%	0.24 [0.18, 0.31]	
Lorenzo D. Botto, 2006	65	821039	17	525813	2.7%	2.45 [1.44, 4.18]	
Lorenzo D. Botto, 2006	89	4688525	62	4073456	3.3%	1.25 [0.90, 1.72]	
Mark A. Canfield, 2005	993	5055906	936	5171501	3.8%	1.09 [0.99, 1.19]	
Subtotal (95% CI)		51247354		60588622	45.7%	0.94 [0.73, 1.21]	
Total events	2360		3592				
Heterogeneity: Tau² = 0.20; Chi² = 190.76, df = 14 (P < 0.00001); I² = 93%							
Test for overall effect: Z = 0.47 (P = 0.64)							
1.2.3 Cystic kidney							
Andrew E. Czeizel, 2004	2	3056	0	3056	0.3%	5.00 [0.24, 104.26]	
Lorenzo D. Botto, 2006	344	5014684	349	8254310	3.7%	1.62 [1.40, 1.88]	
Lorenzo D. Botto, 2006	176	2019160	188	3863382	3.6%	1.79 [1.46, 2.20]	
Lorenzo D. Botto, 2006	143	1909290	36	745946	3.2%	1.55 [1.08, 2.24]	
Lorenzo D. Botto, 2006	145	2503748	265	5933099	3.6%	1.30 [1.06, 1.59]	
Lorenzo D. Botto, 2006	627	14227129	257	5956790	3.7%	1.02 [0.88, 1.18]	
Lorenzo D. Botto, 2006	147	2919355	76	3004926	3.4%	1.99 [1.51, 2.63]	
Lorenzo D. Botto, 2006	322	4593023	113	1940492	3.6%	1.20 [0.97, 1.49]	
Lorenzo D. Botto, 2006	78	2068966	85	3000000	3.3%	1.33 [0.98, 1.81]	
Lorenzo D. Botto, 2006	78	1985899	72	11143868	3.3%	6.08 [4.41, 8.37]	
Lorenzo D. Botto, 2006	46	1117825	32	1034483	2.9%	1.33 [0.85, 2.09]	
Lorenzo D. Botto, 2006	235	2319749	144	5937500	3.6%	4.18 [3.39, 5.14]	
Lorenzo D. Botto, 2006	63	821039	38	525813	3.1%	1.06 [0.71, 1.59]	
Lorenzo D. Botto, 2006	197	4688525	182	4073456	3.6%	0.94 [0.77, 1.15]	
Subtotal (95% CI)		46191448		55417121	44.8%	1.66 [1.26, 2.19]	
Total events	2603		1837				
Heterogeneity: Tau² = 0.24; Chi² = 232.31, df = 13 (P < 0.00001); I² = 94%							
Test for overall effect: Z = 3.56 (P = 0.0004)							
Total (95% CI)		**102570806**		**121566312**	**100.0%**	**1.21 [1.02, 1.42]**	
Total events	9423		10884				

Heterogeneity: Tau² = 0.18; Chi² = 639.31, df = 31 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.24 (P = 0.02)
Test for subgroup differences: Chi² = 10.56, df = 2 (P = 0.005), I² = 81.1%

Figure 3 Forest plot with pooled odds ratios of the effect of supplemented folic acid on offspring CAKUT-subgroup analysis by types of malformations. M-H, Mantel-Haenszel; CI, confidence interval; CAKUT, congenital anomalies of the kidney and urinary tract.
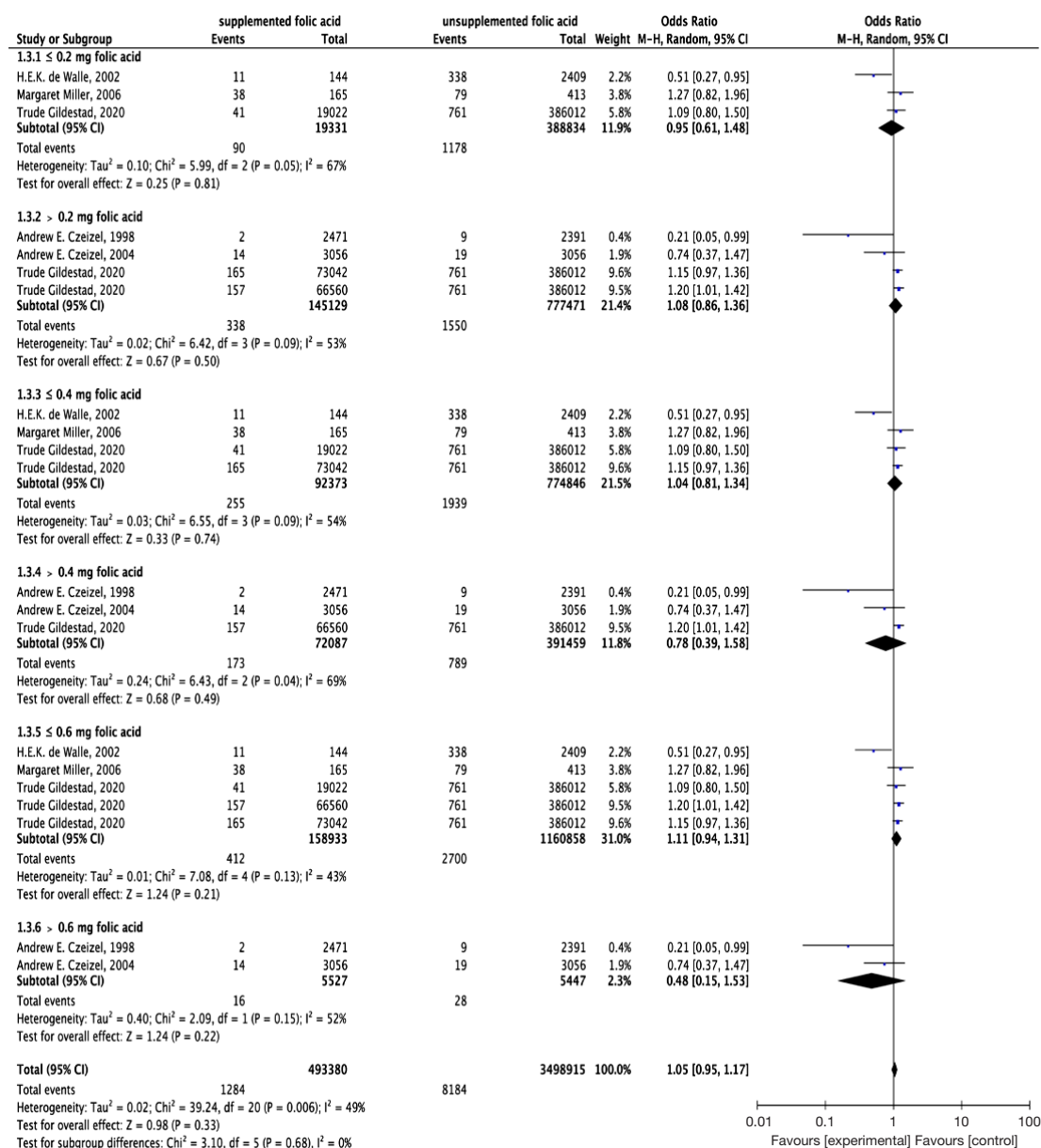
Figure 4 Forest plot with pooled odds ratios of the effect of supplemented folic acid on offspring CAKUT-subgroup analysis by folic acid doses. M-H, Mantel-Haenszel; CI, confidence interval; CAKUT, congenital anomalies of the kidney and urinary tract.

throughout pregnancy, the prevalence of CAKUT in offspring decreased (OR =0.78; 95% CI, 0.39–1.58; P=0.49). When FA supplementation was ≤0.6 mg/day throughout pregnancy, the prevalence of CAKUT in offspring was increased (OR =1.11; 95% CI, 0.94–1.31; P=0.21). At >0.6 mg/day of FA supplementation during pregnancy, the prevalence of CAKUT in offspring decreased (OR =0.48; 95% CI, 0.15–1.53; P=0.22).

Discussion

This meta-analysis clarified that maternal FA supplementation might increase the incidence of renal urinary malformations in offspring, mainly the incidence of cystic kidney. However, different doses of folic acid supplementation did not suggest a significant difference. To date, this is the first systematic review and meta-analysis to focus on the association between maternal FA

supplementation and offspring renal urinary malformations.

Maternal FA supplementation has an obvious protective effect on decreasing the risk of neural tube defects (NTDs) in offspring. However, whether maternal folic acid supplementation has an equal protective impact against birth defects in other systems, such as the renal urinary system, remains inconclusive. Among these birth defects, CAKUT is a series of congenital defects with a complicated etiology. In recent years, with the investigation of massive sample populations, a few high-hazard maternal pathogenic factors associated with CAKUT in offspring were discovered. Bower (9) discovered that mothers without FA supplementation had a high risk for CAKUT in their offspring. Czeizel (16) also discovered that maternal FA supplementation can reduce the risk of CAKUT. However, the Canfield (7) study also suggested that FA use is associated with obstructive urinary tract dysplasia, resulting in an increased prevalence; Godwin *et al.* (8) reported an increase in ureteral obstruction with renal pelvis with FA use (OR =1.45, 95% CI, 1.24–1.70). All of the above findings suggest that whether maternal FA supplementation during pregnancy affects congenital renal and urinary tract malformations in offspring is uncertain. Our final results confirmed that maternal FA supplementation might increase the CAKUT incidence in offspring (OR =1.14; 95% CI, 1.02–1.27; P=0.02). Further subgroup analysis of the CAKUT phenotype in offspring included three groups (hydronephrosis, renal a/dysgenesis, and cystic kidney), and confirmed that maternal FA supplementation/ maternal FA enhancement was related to an increased hazard of cystic kidney in offspring. Although there was only one randomised controlled trial (RCT) and one cohort study included in our research, they were nevertheless suggestive of the results. Caution should be exercised in recommending maternal FA supplementation and in selecting the appropriate dose in patients with a family history of CAKUT.

Currently, in Europe, including Italy, the public health recommendation is that healthy women of childbearing age planning to become pregnant should take an FA supplement containing 0.4 mg per day for at least 4 weeks before conception until 8 to 12 weeks of pregnancy for NTD prevention (18). In addition, the recommendation for preventing NTDs in mothers with epilepsy or diabetes is to take FA 4 to 5 mg per day, which means a higher dose of FA supplementation. European countries have not established mandatory FA-fortified food, and enhanced sources of folate can only be obtained through FA supplementation,

voluntary fortification, and folate-rich vegetables and fruits. Recent studies have not yet determined optimal levels of serum folate for NTD prevention. However, some retrospective studies (19) have shown a dose-dependent approach to NTD prevention, showing that FA 0.4 mg per day reduces the risk of NTDs by approximately 36%, while FA 5 mg per day reduces the risk by approximately 85%. However, such FA supplementation doses have not been clarified regarding other birth defects, such as CAKUT and congenital heart disease. Bortolus (20) designed a multicenter, double-blind RCT comparing the effect of periconceptional FA supplementation at a higher dose (4 mg per day) versus a conventional dose (0.4 mg per day) on reducing offspring birth defects and adverse reproductive outcomes and found no significant difference in the occurrence of offspring birth defects between the two groups (RR =0.80; 95% CI, 0.31 to 2.03); however, 4 mg/day of FA supplementation reduced the incidence of other adverse pregnancy outcomes (RR =0.51; 95% CI, 0.40 to 0.68). To explore the relationship between different FA doses and the occurrence of renal malformations in offspring, this study also conducted a subgroup analysis of the literature with a clear description of the dose of FA and divided the amount of folic acid supplementation into 6 groups: ≤0.2 mg per day, >0.2 mg per day, ≤0.4 mg per day, >0.4 mg per day, ≤0.6 mg per day, and >0.6 mg per day. Unfortunately, no dose-dependent effect was found among the different folic acid dose supplementation groups. The relationship between the FA dose and the occurrence of CAKUT remains unclear and needs further research.

Our study has several advantages. First, this was the first systematic analysis to clarify the relationship between maternal FA supplementation and renal urinary system developmental malformations in offspring. Our study included high-quality articles with large study populations. We graded the evidence for outcomes using the GRADE system. In our studies, benign pregnancy outcomes for renal dysplasia included hydronephrosis, congenital renal dysplasia, and cystic kidney; folic acid doses were also classified. Furthermore, detailed subgroup analyses were conducted to elucidate the correlation of maternal FA supplementation with offspring renal urinary system developmental malformations.

Of course, our study had some limitations. First, few articles describe the effect of maternal FA supplementation on renal urinary system developmental malformations, and multiple birth defects, including renal dysplastic outcomes,

are often reported in one article. At the same time, when we analyzed the effects of maternal FA supplementation on specific renal developmental malformations, the data were limited, and heterogeneity in the outcomes was somewhat difficult to control. We pooled effect sizes using a random-effects model and performed subgroup and sensitivity analyses for primary outcomes. Second, due to the limited literature for final inclusion, this article could not clearly distinguish between FA supplementation before and throughout pregnancy or in early, middle and late pregnancy, making it a possible critical window for further exploration of the effect of FA supplementation on renal dysplasia. Third, the FA supplementation also includes different national and regional FA-fortification policies, including FA supplements, voluntary fortification, and folate-rich vegetables and fruits, which makes it difficult to ensure voluntary and normative fortification of national and regional populations, which may lead to some misclassification of the exposure group. Fourth, there are many genes and potential drug or medication interactions possibly related to CAKUT incidence, which were not considered in this study. Finally, one cohort study and one RCT were included here, which is an important reason for the relatively low level of GRADE evidence. More prospective or experimental studies are needed to provide a higher level of evidence to support the conclusions.

Conclusions

In conclusion, despite the limitations, maternal FA supplementation may be associated with offspring CAKUT, especially cystic kidney. Prescription of FA supplementation for pregnant women should be carefully censored, especially for pregnant mothers with a family history of kidney disease.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://pm.amegroups.com/article/view/10.21037/pm-23-11/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-23-11/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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