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EFFECT OF HIGH DOSE FOLIC ACID SUPPLEMENTATION IN PREGNANCY ON PRE-ECLAMPSIA (FACT): DOUBLE-BLIND, PHASE III, RANDOMIZED CONTROLLED, INTERNATIONAL, MULTICENTRE TRIAL

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Abstract:

To regulate the high dose folic acid supplementation's efficacy for the deterrence of women pre-eclampsia with many risk factors like; twin pregnancy, pre-existing hypertension, type 1 or type 2 pre-pregnancy diabetes, pre-eclampsia in some past pregnancy or BMI ≥35. Randomized, double-blinded international, phase III, multicentre clinical trial.

Through Medline Database records of five countries, seventy obstetrical centers 2464 pregnant women with a risk factor for pre-eclampsia were randomized from 2011 to 2015 (with 1157 placebo group and 1144 folic acid group). Eligible females were randomized to receive either placebo from 8 weeks of conception to 16th week of gestation till the time of delivery or daily folic acid high dose (oral tables of four 1mg).

The major results were pre-eclampsia described as 20 weeks gestation hypertension exhibiting with main proteinuria or ("hemolysis, elevated liver enzymes, low platelets) HELLP syndrome.

Pre-eclampsia happened in 14.8% (169-1114) female in the group of folic acid and 13.5% (156/1157) in the group of placebo (95% CI 0.90 to 1.34; P=0.37, relative risk 1.10). Evidence of difference in between groups is absent for any other severe or neonatal maternal outcomes. Supplementation with folic acid 4.0 mg per day beyond the 1st trimester does not avert pre-eclampsia in female according to high risk for the situation.

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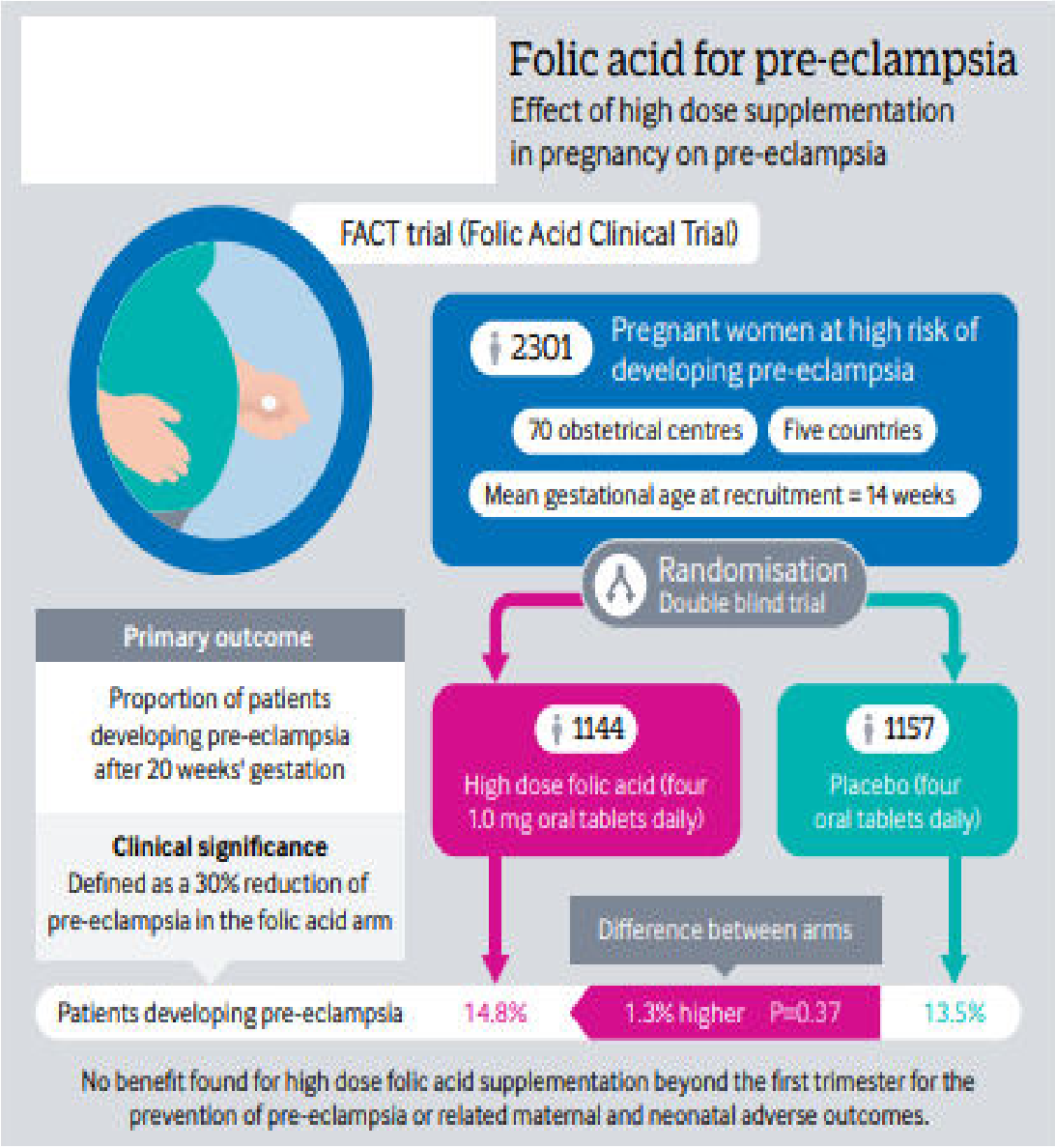
1.0 INTRODUCTION:

Pre-eclampsia is basically a severe medical condition, assuming about 3-5% of pregnancies, specifically accounting for maternal death 35000 per year throughout the globe and significant characteristic in maternal morbidity. Effect of preeclampsia on multi-organ system remains and guide to an elevated severe complication risk in pregnancy. Since the placenta delivery is the specific known cure, pre-eclampsia is preterm delivery, mortality, perinatal morbidity, and long-term incapacity's leading cause (Dehkordi, Shahraki and Lotfizadeh, 2016).

Epidemiological researchers of the link between supplementation of folic acid and the pre-eclampsia of incidence have represented the potential defensive effect, though the results have been unpredictable. In a specific supplementation random trial with a multivitamin holding 0.8 mg folic acid and also pregnancy hypertension with elevated risk populace of females for HIV antibodies, there was a 38% decline was analyzed in the basic composite results of pregnancy hypertension the group of intervention as compared to the group of placebo (El-mani et al., 2016).



(Source: El-mani et al., 2016)

Several other folate forms, comprising 5-methyltetrahydrofolate, have been examined with identical outputs, while antagonists of folic acid have represented the reverse effect, elevated the risk of preeclampsia. This research is based on larger trials about the folic acid supplementation to avert the neural tube imperfections have been suggested throughout the globe in the period of preconception and pregnancy's first trimester (El-mani et al., 2016).

Daily 4.0-5.0 mg is the recommended doses to 12 weeks' pregnancy for females at the affected fetus high risk and 0.4-1.0 milligrams per day for females having low risk. Thought the neural tube ends in 1st trimester, there are two stages preeclampsia disorder, accordingly at first stage happening in the delayed first trimester and similarly 2nd stage happening in the 3rd trimester. High dose of folic acid supplementation in the initial period of pregnancy may support at two stages of preeclampsia growth, and a higher dose in the early second or late first trimester (ELLISON, 2016).

2.0 METHODS:

2.1 Trial design and study population

Covering the different populations of five countries (data gathered through Medline Database) FACT was a randomized, double-blinded, placebo-controlled, phase III for 70 obstetric referral centers. In this trial, we recognized pregnant females to be qualified for contribution with the condition that they must be gestation stage of eight to sixteen complete weeks with an established viable fetus and having the risk factors (at least one) for pre-existing hypertension, pre-eclampsia, pre-pregnancy type 1 or 2 diabetes, pre-eclampsia in past pregnancy, BMI ≥35 kg/m2 or twin pregnancy (Henzel et al., 2017).

BMI measured documentation between 12 weeks before pregnancy and randomization up to the time was needed as eligibility of study. On the contrary, we excluded females if there is any known fetal death or fetal anomaly or a maternal medical complication's history, cancer, epilepsy illicit drug or misuse of alcohol, or any past participation of the same trial, any important past disease and situation which may prevent the utilization of folic acid high dose up to daily 5.1mg (Hernandez-Diaz, 2016).

2.2 Participant recruitment and randomization

The terms and conditions of this trial were already described to eligible females and also present the written informed consensus; we randomized respondents to either placebo or folic acid groups. Data of study were entered into a specific platform (web-based) at every site. The trial intrusion entailed of placebo or 4.0 mg folic acid take as four tablets of 1.0 milligrams daily, from 8-16 weeks gestation until delivery (Hernandez-Diaz, 2016).

2.3 Frequency and Follow up duration

Four in total follow-up visits happened at completed 24 to 26 gestation weeks, gestation completed weeks of 34-36, post-delivery era and 42 days post-partum. At the early visit of the study, information was gathered by maternal medical "Medline Database" record. On every study visit, we also carried out a blood examination, weight, dipstick of urine and fetal wellbeing (Henzel et al., 2017).

2.4 Primary outcome

The basic results were pre-eclampsia, described by using the accepted exploration at the trial commenced time: diastolic BP ≥90 mm Hg on two times in 4 hours or more proteinuria and apart in females at gestation's 20 weeks or greater, or HELLP Syndrome analysis or superimposed pre-eclampsia (Huttly, Wald and Walters, 2017).

Basically, the primary outcome was arbitrated established on the consensus opinion of several investigators. Negotiation was managed before any analysis of statistical data, incognito to the group of treatment, site, and country. We expelled females from primary result investigation who practiced early intrauterine fetal death or miscarriage or withdrew consent (Lassi et al., 2016).

2.5 Secondary outcomes

Pre-specified secondary results comprised maternal death, placental abruption, acute pre-eclampsia with HELLP or convulsion or delivery, premature rupture of membranes, preterm delivery, intrauterine development restriction, antenatal inpatient stay length, spontaneous abortion (or miscarriage) perinatal mortality, stillbirth, neonatal morbidity, neonatal mortality and length of stay in neonatal ICU (Lassi et al., 2016).

2.6 Statistical analysis

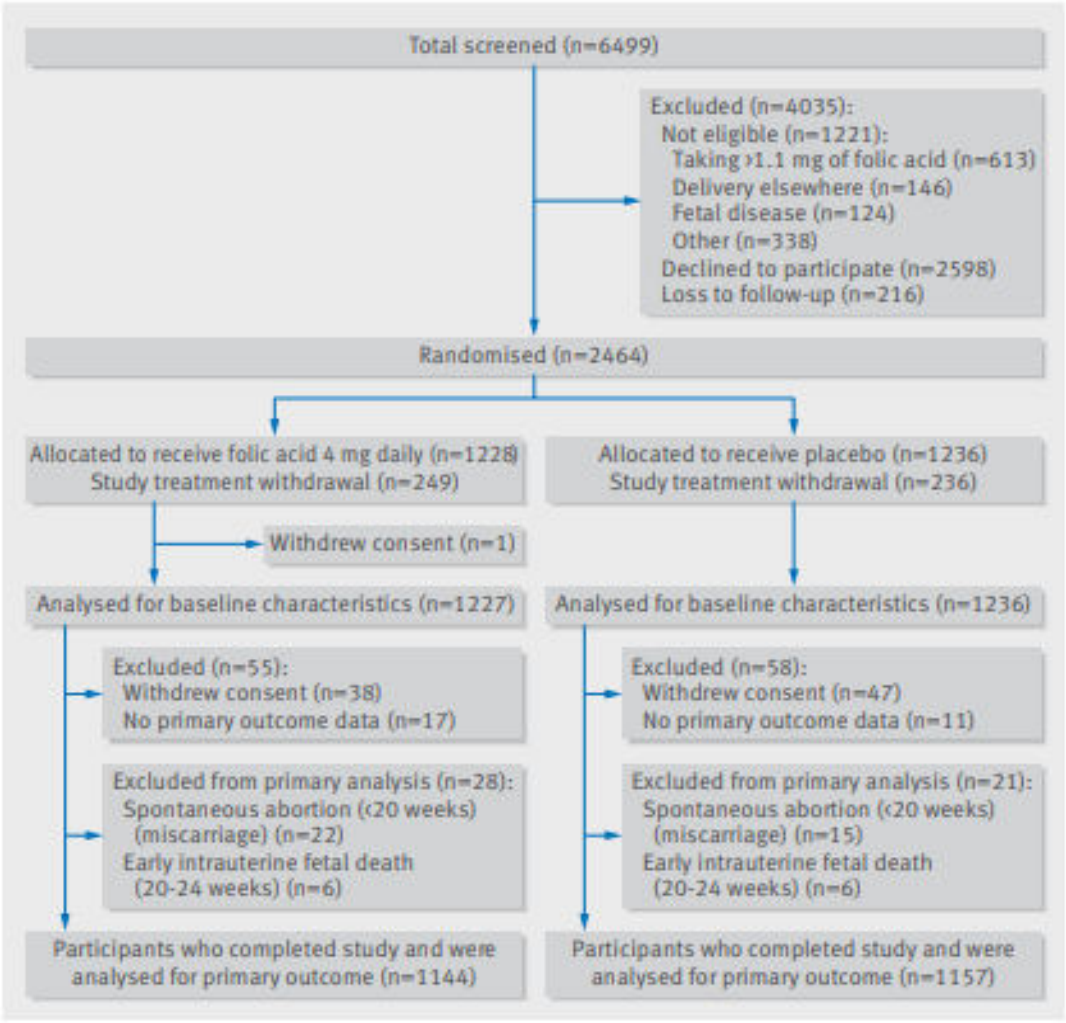
On high-risk pregnant women data basis, we generally projected that a 3656 pregnant women sample was required to perceive a 30% preeclampsia decline from 12.0% to 8.4% and to permit for up to non-adherence 30%, withdrawal lost to follow-up or any unanticipated events. We recalculated the 2464 women sample size which reserved a study power greater than 80% and yet permitted for up to the loss of 10% to withdrawal and follow-up. This research was carried out on a purpose to treat base (Hernandez-Diaz, 2016).

We compared the baseline features, folic acid intake, compliance, and calcium or aspirin based supplementation between placebo and intervention groups. The results between placebo and intervention groups were compared while using $\chi 2$ tests regarding the incidence of pre-eclampsia and unconditional secondary results and *t* tests for continuously disturbed means of secondary results. Several log-binomial regressions was directed on the primary results to regulate for probable perplexing by age, parity and other significant prognostic factors recognized a priori (Huttly, Wald and Walters, 2017).

2.7 Patient Involvement

Though we did not vigorously pursue patient appointment in the growth of this decorum, physician's input was delivered according to a specific survey, advising that their population of the patient would be trial interested and we pursued their suggestion on best performs to roll out the trial. A directing international content expert committee with diverse expertise delivered developmental input of the study results' protocol and trial procedures (Dehkordi, Shahraki and Lotfizadeh, 2016).

The abovementioned committee also analyzed how to reduce the effect on trial participants, like, follow up of the trial visits were organized with antenatal care visits routine. In this research patients were not engaged in research questions' setting or with any results' measures, nor were they interested while establishing recruitment plans or study implementation (Huttly, Wald and Walters, 2017).



(Source: Dehkordi, Shahraki and Lotfizadeh, 2016)

3.0 RESULTS:

3.1 Characteristics of participants

Between 2011 till 2015, 6499 pregnant females were vetted and 3464 of these females were registered in this trial, which 1228 were folic acid randomized and 1236 to placebo. After omitting females who practiced miscarriage (n=37), had no basic results data available (n=28), practiced earl intrauterine fetal death (n=12, gestation weeks 20-24), or extracted consensus before result ascertainment (n=85), signifying a 96.5% rate associated with 2301 females of primary outcome data (Henzel et al., 2017).

A sum of 485 females across both placebo and intervention groups obsolete the treatment of study but endured in the trial and delivered data both for primary and secondary results. The baseline distribution and features of pregnancy were identical between both groups. A high rate of 80% pregnant females in both placebo and intervention groups reported taking a folic acid supplement or folic acid with vitamins. Among the 78.8% (1941) females, who returned research treatment bottles, 75.5% (1465) took at least their pills of 75%, verifying the high amenability rate (Henzel et al., 2017).

Assessments of samples of blood from overall 50 participants (31 in placebo group and 19 in folic acid group) it indicated that folate serum was significantly elevated in folic acid group ("mean 260.1 v 77.8 nmol/L, P=0.008") and folate levels of red blood cell were identical (2700 v 2680 nmol/L, P=0.88") (ELLISON, 2016).

4.0 DISCUSSION:

The outputs of this international randomized managed multicentre trial did not represent evidence that supplementation with folic acid high dose (4.0 to 5.1 milligrams) between 8 to 16 completed gestation weeks and continued up to delivery averts preeclampsia in at-risk females. We regulated this assessment for probable confounders by maternal age, parity, cigarette smoking and established there was no impact of pre-eclampsia prevention of folic acid. When in this research, we examined the impact of folic acid high dose on pre-eclampsia risk by country, there was no divergence in effect was pragmatic (Wen et al., 2016).

4.1 Comparison with other studies

Folic acid supplementation in the time period of pregnancy is now general in different countries of the globe. In this cohort study 2713 (91.9%) appropriated supplements folic acid during pregnancy, and of females who utilized supplementation folic acid, only 20.0% (544) obsolete in the third trimester, therefore 16.5% (447) utilized more than 2.0 milligrams per day. Identical patterns were experiential in the research trial populace, with 80% women that taking folic acid supplements (Wen and Walker, 2016).

High dose folic acid supplementation (basically 4.0 to 5.0 milligrams per day) in pregnant females has already developed extensively beyond the first trimester. Subjective evidence advises that high dose folic acid supplement is happening outside the recommendations for utilization only in initial pregnancy for the preclusion of neural tube flaws, even though the latest Cochrane assessment of folic acid in pregnancy for maternal health results was unable to state on pre-eclampsia remaining to data lack from clinical trials. Caution must always be practiced in treatment recommending before the thorough assessment has been finalized, comprising follow-up of progeny when possible (Henzel et al., 2017).

5.0 CONCLUSION:

At the concluded note, this study includes the elevated risk exploration of pre-eclampsia in mother basically carrying twins and utilizing high folic acid dose and the protective potential effect of folic acid on perinatal death on-going research. Probably most significantly, FACT delivers an exclusive opportunity to keep on the respondents and their offspring to research the impacts of folic acid high dose during prenatal growth on long-term maternal and health of the child, given the probable epigenetic impacts of folic acid.

REFERENCES:

1. Dehkordi, N., Shahraki, A. and Lotfizadeh, M. (2016). Comparison of high dose and low dose folic acid supplementation on prevalence, onset and severity of preeclampsia. *Advanced Biomedical Research*, 5(1), p.192.
2. ELLISON, J. (2016). Effect of supplementation with folic acid throughout pregnancy on plasma homocysteine concentration. *Thrombosis Research*, 4(2).
3. El-mani, S., Mullan, J., Charlton, K. and Flood, V. (2016). Folic acid and iodine supplementation during pregnancy: how much do pharmacists know and which products are readily available?. *Journal of Pharmacy Practice and Research*, 44(3), pp.113-119.
4. Henzel, K., Ryan, D., Schröder, S., Weiergräber, M. and Ehninger, D. (2017). High-dose maternal folic acid supplementation before conception impairs reversal learning in offspring mice. *Scientific Reports*, 7(1).
5. Hernandez-Diaz, S. (2016). Risk of Gestational

Hypertension in Relation to Folic Acid Supplementation during Pregnancy. *American Journal of Epidemiology*, 156(9), pp.806-812.

6. Huttly, W., Wald, N. and Walters, J. (2017). Folic acid supplementation before pregnancy remains inadequate. *BMJ*, 319(7223), pp.1499-1499.
7. Lassi, Z., Salam, R., Haider, B. and Bhutta, Z. (2016). Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. *Cochrane Database of Systematic Reviews*.
8. Wen, S. and Walker, M. (2010). T16.2 Effect of folic acid supplementation in pregnancy on preeclampsia. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, 1, p.S28.
9. Wen, S., Champagne, J., Rennicks White, R. and Walker, M. (2016). OS040. Effect of folic acid supplementation in pregnancy on preeclampsia–Folic acid clinical trial (FACT). *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health*, 2(3), p.198.