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Peri-Conceptional Intake of Folic Acid Supplement to Date: A Medical-Legal Issue

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ABSTRACT

Folic Acid (FA) supplementation during pregnancy represents a so widespread and established recommendation all over the world, to be taken for granted sometimes. As a matter of fact, this vitamin supplement is worldwide recommended mostly during peri-conceptional period for its proved preventive effect on Neural Tubal Defects (NTDs), like spina bifida. However, The biological and clinical potential of FA is reassessing and this represents a hot topic in scientific community, mostly in consideration of the possible medical-legal implications. An overview is mandatory in order to keep in mind FA-related possible benefits and adverse effect and the several regimens for each set of patients in order to reach an even more targeted prescription, avoiding possible unaware mistakes.

Abbreviations: FA: Folic Acid; NTDs: Neural Tubal Defects; RCT: Randomized Controlled Trial; ARTs: Assisted Reproductive Techniques; FAZST: Folic Acid and Zinc Supplementation Randomized Clinical Trial; UMFA: Un-Metabolized Fraction; ASDs: Autism Spectrum Disorders; WHO: World Health Organization; DACH: Deutschland-Austria-Confederation Helvetica; IDA: Italian Drug Agency

Introduction

Folic acid (FA) supplementation during pregnancy represents a so widespread and established recommendation all over the world, to be taken for granted sometimes, being underestimated its potential, which is still being studied [1,2]. To date, in fact, there are still new fields to investigate regarding the prescription and administration methods, which are worthy of further study not only in clinical terms, but also concerning medico-legal obligations and responsibilities. Moreover, nowadays particular attention should be paid to the intake of FA in the preconception period as well as during pregnancy, in order to be able to fully benefit from this supplement. Similarly, the prescribing physician should be aware of the legal pitfalls that a standardized FA prescription might entail rather than a tailored one [1,2]. Let's discuss it in this narrative review, born with the aim to focus on unacknowledged but useful aspects on FA use.

What is Folic Acid

FA represents the synthesized form folate, which is the water-soluble natural form of vitamin B9. FA, as an organic compound,

has the main role in biochemistry take part to single-carbon transfer reactions, like methyl, methylene or formyl group [3]. In biology this translates into FA involvement in certain amino acids transformations as well as in the synthesis of purines and dTMP (2'-deoxythymidine-5'-phosphate), needed for the synthesis of nucleic acid (DNA) and so for cell division and proliferation too [4]. Therefore, FA takes part to biological processes involving all types of rapidly growing cells, mostly like erythropoiesis and making normal-shaped red blood cells preventing anemia, embryo or fetus intrauterine growth preventing birth defects, lowering homocysteine blood level preventing heart disease and stroke, interfering cancer growth [5,6]. FA is a functional food constituent, of which many foods are naturally rich, like: liver, nuts and peanuts butter, dried peas or beans, several types of juice (orang, pineapple and tomato), several types of fruits (orange, avocado, cantaloupe) and leafy green vegetable [7].It is possible to get an adequate amount of FA through a good diet and supplement, this latter is the easiest way mostly in certain conditions in which a major folic acid amount is required, like pregnancy [7]. Indeed, FA benefits are known since 90's, since when, according to BRFSS reports, the main reasons for taking folic acid were birth defect (36,9%), strong bones (19,1%), blood pressure (3,7%), and for the 14,5% all the others described above and for another 25,8% unknown reasons [8].

Neural Tubal Defect Prevention

In 1991 one Randomized Controlled Trial (RCT) demonstrated for the first time that peri-conceptional FA supplementation is able to prevent the recurrence of Neural Tubal Defects (NTDs), from then on US government and European Countries (including Italy) first planned a strategy of food fortification with FA for fertile women [9]. Nowadays worldwide guidelines suggest that fertile women take 0,4 mg folic acid/die before and after conception [10]. A FA relative or absolute deficiency would hinder embryogenesis processes, including neurulation, neural tube properly closing and column and brain development. When spine fails to close completely it occur the so called NTDs, which are: spina bifida (60%), anencephaly (30%) and encephalocele (10%) [10]. Spina bifida is the most frequent NTDs and it is associated with further fetal problems, like hydrocephalusa, clubfoot, vertebral anomalies and renal anomalies. Spina bifida requires surgery 24-48hours after birth, not giving always a complete rehab [10,11]. Generally, NTDs have poor prognosis and are the second most common cause of infant mortality. Its prevalence changed before and after FA fortification, lowering up to 31%-50% all over the world, and to date NTDs occur in 6-10 out of every 10.000 births [11,12]. Despite of this latter NTDs still leads the world health systems to bear high costs, involving at the same time the financial, the physical and the emotional fields [11,12]. According to a CDC data an average estimated lifetime cost of 532,000 dollar for each infant born with spina bifida and estimated 19 million dollars every year to resident lifetime costs associated with spina bifida. Moreover, considering that NTDs are the leading cause of childhood paralysis, we have to add all the supplemental costs linked to NTDs-related disability, like harms or legs paralysis, bowel and bladder control problems, learning disabilities, hydrocephalus, surgical procedure. Equally relevant are the emotional implications and resulting costs associated with NTDs such as: miscarriage, stillbirth, infant mortality (meant as death before 1st birthday), disability [11,12]. However, it will have to study further factors, which increase NTDs risk acting synergistically with folic acid deficiency, like: family history of NTD, a previous pregnancy affected with NTD, maternal insulin-dependent diabetes, maternal obesity, lower socioeconomic/educational level, race/ethnicity, geography, exposure to high temperatures in pregnancy, anti-epileptic drugs, alcohol drinking and passive smoking [13,14]. To date known risk factors account only for <50% of NTDs cases [14].

Improving Couple's Fertility Effect

Even if according to female biological clock the best time to get pregnant is between late 20s and early 30s, during the last decades the women average age to begin to seek pregnancy has increased so as to have to resort more and more frequently to Assisted Reproductive Techniques (ARTs). About that FA would significantly enhance couple's reproductive capacity, as it is being investigated in medically assisted procreation scenarios. Gaskins et al in 2014 demonstrated that supplemental FA is related to a higher probability of live birth among women undergoing ART. However, they observed that such good outcomes occurs at FA intake levels ranging around 800-1500 micrograms/day, much higher than those currently recommended for NTDs prevention, but substantially lower than those prescribed to some women seeking preconception care or undergoing infertility treatment in other parts of the world [15]. Just a year later a trial of the same group of researchers reports that the higher serum concentrations of FA (>26.3 ng/mL) and vitamin B12 (>701 pg/mL) before ART treatment correlates the higher live birth rates among population exposed to pre-conceptional supplementation [16]. This finding suggests that a single vitamin supplement, such FA, would not be able to significantly improve responsiveness to ART and so reproductive outcome among infertile women alone, but that it would be the result of a synergistic interaction between several macronutrients [16]. The broadening of the search spectrum found a specific link between maternal nutrition and fertility. 2019 research demonstrates that the higher pretreatment adherence to a so called "pro-fertility diet", the higher live birth rate after ART.

According to this study, conducted on US infertile women, the so commonly recommended Mediterranean diet may not be the most appropriate one [17]. However, a recent Italian meta-analysis

conducted by Paffoni et al, using the red blood cells folate threshold specifically indicated to prevent NTDs, reveals that there aren't sufficient data to conclude on the relationship between women FA status and probability of success of ART treatments [18]. On the contrary other subsequent studies shift from a woman-centric view in terms of FA supplementation to a couple-based preconception care concept. For the first time Martin-Calvo et al show the link between paternal preconception FA intake and a slightly prolongation of gestation among live births achieved through ART [19]. Hoek et al remark the matter of peri-conceptional paternal folate status, which also significantly correlates with embryonic growth trajectories in spontaneously conceived pregnancy [20]. However, have not yet been identified possible co-factors, which FA benefits on male fertility. In example the zinc supplementation in addiction to FA for male partners does not significantly improve couples live birth rate, as reported by several studies, including FAZST (Folic Acid And Zinc Supplementation Randomized Clinical Trial) [21,22]. According to this latter zinc supplementation does not alter sperm DNA methylation, therefore showing no improvement on semen analysis parameters and so on reproductive ability too [22]. Instead, the systematic review, conducted by Majzoub, et al. [23] in 2018 and based on 26 studies, manages to reveal the role of several types of antioxidant in terms of male and couple infertility. FA and other most used antioxidants on the market, like the mentioned above zinc, vitamin E, vitamin C, carnitine, N-acetyl cysteine, co-enzyme Q10, selenium and lycopene, would improve semen parameters and function and ART outcomes at all [23]. The contrasting results could not be justified by a FA-centric view but by a multifactorial view, shifting the research hot spot from a single agent supplementation to a supplementation regime, whose composition and optimal dosages for each single element are still to be defined and shared.

Possible Neurological E Psychiatric Condition FA-Related

To date there are knowledge gasps in understanding the metabolic and clinical effects of FA at all, both for good and for bad. The axiom, according to which regardless dosage FA is completely safe for woman and fetus, has been questioned. Some researchers are suggesting a correlation between uncertain etiopathogenesis pathologies and FA, whose widespread intake surely makes the statistical conclusions reported questionable [24]. A prolonged overdose of FA can harm woman and/or fetal neurological system through its Un-Metabolized Fraction (UMFA), causing adverse effect dose-related and almost always reversible after suspension [24]. In literature is described only one case of death following acute consumption of FA exists, consisting in a suicide of a pregnant woman by voluntary taking for long time very high doses of FA [25]. About that certainly a weight has given to some studies mentioned by international scientific societies. In example RCOG highlights on a possible association between FA supplementation and Autism Spectrum Disorders (ASDs) risk. Indeed, higher maternal plasma folate levels (>60.3nmol/L) could increase up to 2.5 times ASDs risk [26]. Maternal self-determined higher FA doses could be due to the anxiety of first pregnancy, as a matter-of-fact ASDs-affected children are more likely first-born [27]. Moreover, a recent prospective study finds a direct correlation between umbilical cord UMFA levels and ASDs risk, which is mostly significant in Black children [28]. Anyway, to date there aren't enough reliable data to confirm this link. On the other hand, peri-conceptional FA intake at the NTDs prevention daily dose of 400mcg should be protective both for ASDs for the baby, mostly in case of high prenatal air pollution exposure, and for perinatal depression for the mother [26,29,30].

FA Intake: Who, When and How

Despite the recommended dietary allowance for FA varies from one country to another, since 90's a FA-rich dietary regimen recommendation is issued by all public health system in the world. The FA daily intakes through food recommended for women during childbearing age and pregnancy, respectively, according to different geographical areas and societies are: 400mcg and 600mcg for IOM (US Institute of Medicine) and WHO (World Health Organization); 400mcg and 500mcg for NNR (Nordic Nutrition Recommendation from the Nordic Council of Ministers); 300mcg and 550mcg for DACH States (Deutschland-Austria-Confederation Helvetica) [31]. The Italian National Institute of Health (ISS) suggests a FA intake equal to 400mcg/die for women who are not trying to get pregnant, 600mcg/die for women who are pregnant or trying to get so and 500mcg/die during breastfeeding period [32]. The mandatory FA food fortification approved by some countries is still object of discussion to date in many others because of the possible and partially unknown high dose related adverse effects, like in Italy. ISS states that FA average dietary intake is almost adequate for the general population, but not for pregnancy [32]. Therefore since 90's FA supplementation for NTDs prevention is worldwide shared and promoted for women during peri-conceptional period. Almost all major national and international scientific societies, including WHO and CDC, recommend a FA supplement of 400mcg/die, except for Brazil, which suggest 5mg/die, and South Africa and Singapore, which do not mention any dosage and refer to the health-care provider [12,31,33].

There are not uniformity on the exact temporal window of peri-conceptional FA supplementation definition, ranging from 12weeks to 4weeks before conception the start and from first trimester to the end of pregnancy the end [32,34-36]. ACOG and SIGO suggest starting FA intake one month before conception and during the 12 week of pregnancy without interruption [34,35], RCOG, instead, does not specify since when during the pre-conceptional period

it should be started and recommends to continue up to 13wks of pregnancy [36]. Women with a previous NTD-affected pregnancy have higher risk of recurrence and so they need a ten times higher dosage of FA, as reported by several countries and health organization. In example the higher FA dose is around 4-5mg, according to ACOG, RCOG and SIGO, and 5mg for WHO ([31-36]. Many other countries either do not specify which FA dosage or even have no specific recommendations at all in this patient set [31]. The NTDs higher risk group also include women women who are familiar with neurological diseases and malformations, who are taking anti-epileptic drugs and all the conditions in which FA bioavailability is significantly reduced: malabsorption diseases, mostly celiac one, and pre-gestational diabetes and/or obesity [35]. There is an inverse interaction between BMI and serum FA levels, leading to a short-term FA pharmacokinetics change and so to a reduced amount of FA available to developing of trophoblast first and embryo and placenta then [37]. This could be explained why obesity is an independent risk factor for NTDs [37]. Moreover overweight, through mechanisms not yet fully known, is also associated with pregnancy complications (preeclampsia and preterm birth), female sterility and infertility and poor ART outcomes, which are all conditions possibly related to a low amount of FA. Surely, as WHO states, a higher daily dose of FA according to the definition of obesity base on BMI significantly improve reproductive capacity [38].

FA Prescription Modalities

The FA NTDs prevention role it has imposed it over time and throughout the world as a necessary and impregnable element of implementation during childbearing age and pregnancy to such an extent that sharing by world guidelines has spread its wide use and demand. The increasingly numerous data give so much credit to FA, that it is practically considered more than a vitamin a "drug". As a result, many national policies agreed in making peri-conceptional FA supplementation free of cost [39]. According to IDA (Italian Drug Agency) in Italy, our area of main interest, a 120 tablets pack of FA 400cgr each or 5mg each, according to the set of patients, can be provided totally free fo charge through medical prescription [10].

Medical-Legal Prescription Issue

A major stir sparked a recent ground-breaking legal case on FA deficiency-related fetal malformation and corresponding medical liability: in 2021 a paralympic athlete won against her mother's physician for his inadequate advice on FA peri-conceptional intake that led to her spina bifida [40]. Many are the unusual and innovative aspects of this case, first of all making scientific community re-focusing on FA in a historical moment in which its prescription and assumption seemed to be fully consolidated, almost taken for granted, without risks for both parties. For the first time a not only medical but also legal correlation is established between the most common type of NTD, spina bifida, and the non-prescription of FA not so much in pregnancy as in the pre-conceptional period. Therefore, in terms of medical liability the so called "wrongful act" is the is the negligent advice, meant as lack or inadequate FA prescription, during pre-conception consultation, which definitively expands the "FA and pregnancy" binomio. As a matter of fact, it is not always perceived as mandatory the pre-conceptional prescription of FA, nevertheless it is suggested by national and international guidelines, as reported above. However, it should be so since the moment when the woman tells her physician she's trying to get pregnant and it is deductible on the basis of the following considerations. Neural tube closes by the 28th day of conception, when almost all pregnant women do not know they are and, if there has not been an adequate preconception counseling, this delays FA intake start long after conception, increasing NTDs risk [9].

Indeed, to date, FA supplement for women in childbearing age is not so established as we commonly think, even in industrialized countries. In example according to a recent Italian survey less than half (43.4%) women takes FA before becoming pregnant, regardless they are trying to conceive or not, and almost all of them belong to high educational level and have received preconception counseling. Anyway, the level of information and knowledge about the benefits of this vitamin is inadequate also among women who plan the pregnancy [2]. Similar evidence also emerges from the reports of the CDC [12]. It is clear that the current national policies are lacking in terms of information and education, and it should both enhance communication campaigns (web, newspaper, TV or leaflets) to population and, at the same time, raise awareness among health operators. Periodic courses and meetings can help physicians acquire more knowledge and so avoid mistakes. It is crucial to know current guideline and their corrispettive updates in order to apply them to the best. The concept of a tailored prescription should be applied also in case of FA, choosing the right regimen on the basis of patient's clinical background, as stated above, without forgetting the relevance of an exhaustive counseling. As a matter of fact, on one hand a FA underdosing due to an inadequate "standardized prescription" is both medically and legally equal to a miss prescription, because in both cases the insufficient blood FA levels reached significantly increase NTDs risk [9]. On the other hand, as discussed above, an overdosing of this vitamin, to date we know, could not be completely devoid of adverse effects, like psychiatric and neurological conditions [24].

In both cases by a legal point of view the main role has the informative counseling. Although between conditions of unknown etiopathogenesis, like ASDs, and FA the cause-effect relationship is still being defined and understood, medical liability would exist if the excessive vitamin intake can be correlated to an inadequate information on the possible risks to the mother and fetus. To date every physician should keep in mind that, even in case of a

vitamin prescription like FA, indispensable but not safe at all, the informative counseling should be complete and clear, and it should be at the same time completely and clearly understood by the patient. Only in this way it is possible to reach a good compliance to therapy, avoiding both lack or excess of assumption for the patient and so medical complications and legal litigation for the physician. Maybe a consensus signed by both parties could be a proposal for the future, although this can make medical practice safe but cumbersome! Overlapping considerations could be made in case of pre-conceptional counseling and FA prescription for infertile couple undergoing ART.

Having confirmed, also in this case, the relevance of a correct information before prescription, the emerging but still unclear effect of FA on reproductive capacity make inconsistence any legal recourse in case of miss or inadequate FA intake and ART failure [15,41]. Indeed, any litigation has to be contextualized in the scientific scenario of that specific historical moment and to date the correlation between NTDs and peri-conceptional FA supplementation represents the most investigated and the stronger association reported in literature, therefore the only one with a medical-legal significance. Surely the need of higher doses in certain sets of women represents a relatively new field of application not only by a clinical point of view, but mostly by possible litigations and legal speculations. Concluding has to remember that the so aimed tailored prescription cannot disregard the physician's freedom to not strictly follow guidelines. Indeed if, according to the physician evaluation, these recommendations do not represent the best care for the specific case of the patient, the health operator has the duty to choose differently [42-44]. In law the acknowledgment of non-binding nature of the guidelines is used not to justify a conviction, but to affirm the possible correctness of the doctor's behavior, experience and good medical practice acquire an own value [42-44]. In Italiy this is set by "Gelli-Bianco" law, but similar legal references are also found in other legislatures of industrialized countries [42-44].

Conclusion

The biological and clinical potential of FA is reassessing, and this represents a hot topic in scientific community. All the FA benefits, proved or not, are pieces of a puzzles, where the other pieces could be co-factors, which sometimes are unknown, underlying several and sometimes unknown bias. Ideologically speaking, as well as the FA intake is not said to guarantee the related benefit, in the same way how much is it possible to attribute unfavorable outcomes to the lack of or erroneous intake and/or prescription of folic acid? And moreover, how can the physician protect himself/herself from this? Surely all these speculations can actually lead to practical litigation. The emerging evidence are questioning the established knowledge on FA and it is health operators duty to inquire about in order to achieve an always better medical practice through a good counseling and a tailored prescription.

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