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Commentary

Dietary supplement intake during pregnancy; better safe than sorry?

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ABSTRACT

Consumption of dietary supplements and specifically niche products such as supplements targeting pregnant women is increasing. The advantages of dietary supplementation during pregnancy with folic acid have been established, but health effects of many other supplements have not been confirmed. EU and US legislation on dietary supplements requires the product to be safe for the direct consumer, the mother. Long-term health effects for the fetus due to fetal programming (*in utero* adaptation of the fetal epigenome due to environmental stimuli such as supplementation) are not taken into account. Such epigenetic alterations can, however, influence the response to health challenges in adulthood. We therefore call for both conducting research in birth cohorts and animal studies to identify potential health effects in progeny of supplement consuming mothers as well as the establishment of a nutrivigilance scheme to identify favorable and adverse effects post-marketing. The acquired knowledge can be used to create more effective legislation on dietary supplement intake during pregnancy for safety of the child. Increasing knowledge on the effects of consuming supplements will create a safer environment for future mothers and their offspring to optimize their health before, during and after pregnancy.

1. Introduction

The popularity of dietary supplements, in this paper defined as sources of concentrated micro- or macronutrients, is rising together with an increasing interest of consumers in potential health enhancing foods (Euromonitor International, 2015; Menrad, 2003; Teichner and Lesko, 2013). Especially niche products, such as dietary supplements that target women of reproductive age and pregnant women, increased their market share over the past decade. For example, from 2010 to 2015, the multivitamin market yearly grew 2 to 19 percent in the eight countries with the highest sales of multivitamins (UK, Brazil, USA, Russia, Mexico, Italy, South Korea and China). In the UK alone, the sales of multivitamins targeting pregnant women grew approximately two percent in these five years, ending up representing 17% of the total multivitamin market in the UK (Schmidt, 2015). Although the availability of epidemiological data is limited, cross-sectional and cohort studies suggest an increase in daily use of supplements (Kim et al., 2014; Radimer et al., 2004; Sullivan et al., 2009). Different studies report that females use different dietary supplements more often than men and especially those persons with increased interest in health were more regularly consumers of dietary supplements (Bailey et al., 2011; Dickinson et al., 2014; Radimer et al., 2004; Rock, 2007). Additionally, in specific subgroups including athletes and long-term cancer survivors at reproductive age, the use of dietary supplements has increased (Knapik et al., 2016; Velicer and Ulrich, 2008; Wardenaar et al., 2016).

The beneficial effect of dietary supplementation before and during pregnancy has only been established for folic acid: folic acid is important for growth and development of both the fetus and maternal tissues and a sufficient intake of folic acid can be guaranteed by supplementing the diet (De-Regil et al., 2015; EFSA NDA Panel, 2009; Eichholzer et al., 2006; Kaiser and Allen, 2008). In various countries, foods are (required to be) fortified with folic acid, whilst the European strategy is to advise the target group (women with the intention to become pregnant and pregnant women) to supplement their diet (Czeizel et al., 2013). Whereas fortification can reach a broader public, it is suggested to expose the general public to too high amounts of folic acid while a large part of the target group may still not meet their recommended daily intake (Czeizel et al., 2013; Osterhues et al., 2013). Women of childbearing age and pregnant women have been reported to increasingly use dietary supplements with other ingredients such as the omega-3 polyunsaturated fatty acid docohexaenoic acid (DHA), calcium, vitamin D, zinc and multivitamins, but also with herbal ingredients such as Echinacea and ginger (Buppasiri et al., 2015; Cave et al., 2016; De-Regil et al., 2016; Imhoff-Kunsch et al., 2012; Ota et al.,

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2015; Picciano and McGuire, 2009; Tsui et al., 2001). However, when a woman is not malnourished during pregnancy, the use of supplements other than folic acid is not proven to be beneficial and its consumption is questionable (Darnton-Hill and Mkparu, 2015; Ladipo, 2000). The maternal diet before and during pregnancy, and even during breastfeeding, has been shown to induce phenotypic changes in offspring which may affect the offspring's health status. Obviously, dietary components can elicit such alterations through the placenta and postpartum through the nutritional values of breast milk, but these studies did not unveil clear cut relationships between the intake of specific nutrients by the mother and health status of their children (Hambidge et al., 2014; Netting et al., 2014; Ramakrishnan et al., 2012).

The safety of such dietary supplements consumed during pregnancy is often not specifically studied (Friedman, 2000; Schweitzer, 2006). Although teratogenic effects of compounds are important in safety assessments (European Parliament and Council of the European Union, 2015), the effects of supplement intake on the long-term health of the fetus seems to be addressed to a much lesser extent. It is however generally acknowledged that the dietary intake (both the quality and the quantity of the diet) and dietary status of pregnant women can affect the development of the fetus which subsequently influences health in adult life (Godfrey and Barker, 2001; Lillycrop and Burdge, 2014). This is exemplified by dietary supplementation with folic acid during pregnancy: whilst supplementation in the first trimester of pregnancy is beneficial for health of the offspring, using folic acid supplements later in pregnancy is suggested to increase the risk to develop allergic diseases and asthma (Eichholzer et al., 2006; Whitrow et al., 2009).

With the increasing awareness about fetal development being influenced by the maternal diet, this paper illustrates how food supplement safety is regulated and why long-term safety is important to be taken into account in safety regulations.

2. Regulating dietary supplement safety

Safety is key in the regulation of dietary supplements. Rules and regulations dealing with dietary supplement safety do however not seem to consider the consequences that consuming such products can have on the offspring of the consumer. In Europe, dietary supplements are regulated by Directive 2002/46/EC, the so-called Food Supplement Directive (FSD) (European Parliament and Council of the European Union, 2002). The FSD defines food supplements as '*concentrated sources of nutrients or other substances with a nutritional or physiological effect*', which are aimed to supplement the normal diet (European Parliament and Council of the European Union, 2002). Medicinal products are specifically excluded under this Directive. Since dietary supplements are categorized as food products, these supplements must comply with other relevant food legislation. The framework regulation concerning foods, the General Food Law (GFL), describes food safety as one of the general principles for food products to be allowed to be placed on the market (European Parliament and Council, 2002). Although the GFL does not provide a definition for food safety, food is described to be unsafe when a product is (a) injurious to health or (b) unfit for human consumption (European Parliament and Council, 2002). In determining whether a product is injurious to health, Article 14 (4) (a) of the GFL specifies that effects on subsequent generations should also be assessed (European Parliament and Council, 2002), next to the short- and/or long-term effects on the direct consumer. Since no specific requirements are however mentioned, this article leaves room for interpretation.

In the United States, the Dietary Supplement Health and Education Act of 1994 (DSHEA) regulates food supplements separately from conventional foods and food additives (Dietary Supplement Health and Education Act of 1994; U.S. Congress). The DSHEA defines supplements as '*any product which contains one or more dietary ingredients such as vitamins, minerals, herbs or other botanicals, amino acids or other ingredients used to supplement the diet*' (Dietary Supplement Health and Education Act of 1994, n.d.). Although food products should be safe when they are available for sale, no specific safety dossier is required before dietary supplements are placed on the market. The DSHEA gives the Food and Drug Administration (FDA) in the USA the authority to safeguard the public from unsafe products (Dietary Supplement Health and Education Act of 1994, n.d.; U.S. Food and Drug Administration, 2014). Therefore, adequate information must be provided to the FDA before a new dietary ingredient can be brought to market and when the FDA shows that the dietary ingredient poses a '*significant or unreasonable risk*' to consumer safety, the product can be removed from the market (Dietary Supplement Health and Education Act of 1994, n.d.). Currently, however, the long-term effects of dietary supplements consumed during pregnancy or during breastfeeding are insufficiently known to make a proper decision about potential risks and consumer safety. In Europe, only new ingredients or products produced by new techniques are subject to the safety review of the European Food Safety Authority (EFSA), a crucial aspect in the pre-market authorization by the European Commission for such a novel food under the Novel Food Regulation (Regulation (EU) 2015/2283) (European Parliament and Council of the European Union, 2015; Turck et al., 2016). The European Commission has described in their recommendation that the wholesomeness of food products, influenced by *i.a.* the nutritional, toxicological and metabolic properties of a product, is key in assessing the authorization of a novel food (European Commission, 1997; Turck et al., 2016). Next to considering the nutritional implications of a novel food, this recommendation also suggests to take short and long term effects of consuming a novel food into account and to pay specific attention therein to groups with specific nutritional requirements, such as pregnant and lactating women (European Commission, 1997). The health effects of offspring in later life do however not seem to be taken into consideration when safety is tested. As the effects of the maternal dietary status and maternal consumption during pregnancy on the development of the fetus become more apparent, the question arises how these findings can be incorporated in legislation, and specifically in dietary supplement regulation.

3. Fetal programming

Before birth, the fetus is affected by various environmental factors such as maternal dietary status, food intake or the intake of dietary supplements by the mother (Fig. 1). The fetus is thought to adapt to these *in utero* circumstances by making changes to the epigenome that are potentially necessary for survival, which can persist in later life (Gicquel et al., 2008; Godfrey and Barker, 2001; Vanhees et al., 2014). In short, the epigenome includes various chemical changes to the structure of DNA without changing the underlying DNA sequence. These chemical changes can be either on the DNA bases (e.g., methylation of cytosine in CpG sequences) or on proteins that are involved in folding the DNA (e.g., histone modifications). These epigenetic modifications are involved in regulating gene expression and therefore affect growth and tissue differentiation, especially in the developing child. Moreover, these modifications can be passed down to the offspring via transgenerational epigenetic inheritance. The DNA sequence in the genome is largely static within an individual, but the epigenome is dynamic and can be altered by environmental conditions, especially by dietary habits (Vanhees et al., 2014). These adaptations to the environmental circumstances by the fetal epigenome may result in altered structures and functioning of the organism, which is also known under different terms, including 'phenotype induction', 'fetal programming' (Burdge et al., 2007; Gicquel et al., 2008; Godfrey et al., 2013; Godfrey and Barker, 2001; Vanhees et al., 2014) or the 'Developmental origins of (adult) health and disease' (DOHAD) hypothesis (47–50). Since different organ systems develop on various critical time points, environmental stimuli or triggers can influence the development of the fetus differently (Al-Ghazali et al., 1989; Barker, 2012; Chmurzynska, 2010;