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# International expert consensus on micronutrient supplement use during the early life course

Irene Cetin<sup>1,8</sup>, Roland Devlieger<sup>2,3</sup>, Erika Isolauri<sup>4</sup>, Rima Obeid<sup>5</sup>, Francesca Parisi<sup>1,8</sup>, Stefan Pilz<sup>6</sup>, Lenie van Rossem<sup>7,9</sup>, Maternal Nutrition Delphi Study Group and Régine Steegers-Theunissen<sup>7\*</sup>

## Abstract

**Background** Growing evidence demonstrates that maternal nutrition is crucial for the health of the mother-to-be, and early life course of the offspring. However, for most micronutrients, guidelines are inconsistent. This Delphi study aimed to investigate the level of expert consensus on maternal nutrition and micronutrient needs during preconception, pregnancy and lactation.

**Methods** We conducted a two-round web-based Delphi survey on various topics including general approaches to diet and supplement use, and existing guidelines. For the periods of preconception, pregnancy and lactation, questions focused on the importance and strength of evidence for supplement use with the following micronutrients for low- and high-risk populations: folic acid, choline, iodine, magnesium, calcium, iron, selenium, docosahexaenoic acid (DHA), and vitamins B1, B2, B6, B12, D and K.

**Results** Thirty-five experts participated in the panel, who were healthcare professionals (HCPs), researchers and joint HCP-researchers with expertise in nutrition, gynaecology and/or obstetrics. Panellists reached consensus on the importance of diet and dietary supplement use during pregnancy and agreed on the lack of clarity and consistency in current guidelines, and the need for education in these areas for HCPs, pregnant people and the general population. For general low-risk populations, there was consensus on the importance of supplement use with iron and vitamin D from preconception through lactation, with folic acid and iodine from preconception through the second and third trimesters, respectively, with DHA from the first trimester through lactation and with calcium during lactation. Panellists agreed that the evidence for supplement use with each of these micronutrients during these phases to improve outcomes and/or foetal development is strong, except for vitamin D (preconception), DHA (first trimester), and iron (both periods). There was also consensus that supplement use advice should be tailored for people following vegan/vegetarian diets, restricted diets due to food intolerances, obesity, polycystic ovary syndrome, diabetes mellitus, and previous nutrition-related pregnancy complications.

\*Correspondence:  
Régine Steegers-Theunissen  
r.steegers@erasmusmc.nl

Full list of author information is available at the end of the article



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**Conclusion** The findings revealed robust consensus on various aspects of maternal nutrition, including the need for education, the lack of consistency in current guidelines on supplement use, the importance of supplement use across specific phases of pregnancy and the at-risk groups requiring tailored approaches.

**Keywords** Maternal diet, Vitamins, Trace-elements, Preconception, Pregnancy, Lactation, Guidelines

## Background

The preconception period and pregnancy are critical periods in the early life course of two generations, marked by significant physiological changes [1]. As the maternal body prepares for pregnancy and adapts to support foetal growth and development, the demand for certain nutrients increases [2]. Accumulating evidence suggests that nutrients, especially micronutrients, play a crucial role in maternal health throughout the reproductive period and beyond [2]. Deficiencies can impact fertility, the course and outcome of pregnancy, and the lifelong health of both the mother and child [2–6].

Although certain nutrients are widely recognised and incorporated into guidelines for intake and/or supplement use, debate continues around their significance at different pregnancy stages, while others are less frequently highlighted [2, 7, 8].

Folate (vitamin B9) is a recognised micronutrient before and during the first trimester of pregnancy [9], as folic acid has been found to reduce the risk of neural tube defects (NTDs) and potentially other adverse outcomes [10]. However, the benefits of continuing folic acid supplement use later in pregnancy, the use of high dosages, and its long-term health impacts on mother and child are not fully clear [11].

Iron is another commonly acknowledged micronutrient for which demands increase during pregnancy [4, 12, 13]. Despite its recognised role in foetal development and maternal haematopoiesis, concerns around potential iron overload have resulted in varied recommendations [4, 12, 14]. Several studies support the role of iodine in foetal thyroid and neural development [15], and the significance of vitamin D for bone health and various pregnancy outcomes [16, 17]. The essential nutrient choline is crucial for foetal health and brain development. The evidence on the impact of sufficient choline intake during pregnancy and lactation on foetal and infant health is emerging. Growing evidence also suggests that higher maternal choline intake is associated with a lower risk of NTDs in the offspring [9, 18, 19]. This raises the question as to why choline is not commonly emphasised in dietary recommendations for these critical periods. Similarly, docosahexaenoic acid (DHA), which is associated with foetal neural development and a reduced risk of preterm birth (PTB) [20, 21], and calcium, which has been associated in some studies with foetal bone health and prevention of pre-eclampsia [9, 22], are not as widely recommended.

It is confusing that the recommendations for micronutrient supplement use vary between guidelines (summarised in Additional File 1). For example, for iron, the US Institute of Medicine (IOM) set the recommended dietary intake (RDI) at 27 mg/day during pregnancy [23], whereas the European Food Safety Authority (EFSA) and the Standing Advisory Committee on Nutrition (SACN) have the same RDI for pregnant and lactating women, and non-pregnant women of reproductive age (16 mg/day and 14.8 mg/day, respectively) [24]. In addition, whilst the World Health Organization (WHO) recommends a daily universal supplement with iron (30–60 mg) [25], routine iron supplement use is not recommended in certain countries, such as the UK and Italy [26, 27]. For iodine, the EFSA has set the adequate intake at 200 µg/day during pregnancy and lactation compared with 150 µg/day for adult women who are not pregnant or breastfeeding. The American Thyroid Association and Australia and New Zealand national guidelines recommend that women who are planning a pregnancy, or who are currently pregnant or breastfeeding, should have a daily oral iodine supplement containing 150–200 µg of iodine [28, 29], and the German national consensus and German Federal Institute of Risk Assessment (BfR) recommend that pregnant and breastfeeding women should use a supplement with 100–150 µg/day [30, 31], whereas the WHO and United Nations Children's Fund (UNICEF) recommend universal salt iodisation to improve iodine status [32]. For vitamin D, recommendations during pregnancy vary considerably. For example, the IOM and the EFSA have an RDI of 600 international units (IU)/day (15 µg/day) [33, 34], D–A–CH (Germany, Austria, Switzerland) nutrition societies recommend 800 IU/day (20 µg/day) [35], and the Endocrine Society in the US and Central European expert guidelines recommend 1500–2000 IU/day (37.5–50 µg/day) [36, 37].

Beyond recommendations for specific micronutrients, there are broader questions surrounding overall approaches to diet and supplement use during pregnancy. Factors such as individual needs, pre-existing health conditions and lifestyle choices can influence nutritional requirements and are frequently debated [6].

Given the recognised importance of maternal nutrition, combined with the ongoing debates and heterogeneous recommendations, there is a need to explore expert opinions regarding knowledge gaps, unmet scientific and educational needs, and state-of-the-art knowledge on maternal nutrition. The Delphi method provides a robust

approach for determining consensus among experts [38], especially in situations where there is limited evidence and expert opinion is valuable [39]. Through iterative surveys, the Delphi method can be used to gather and refine expert perspectives, working to build consensus and identify common areas of agreement and disagreement. The insights gained can then help inform healthcare professionals (HCPs) and target groups, assist in implementation in clinical practice, and be used for future research.

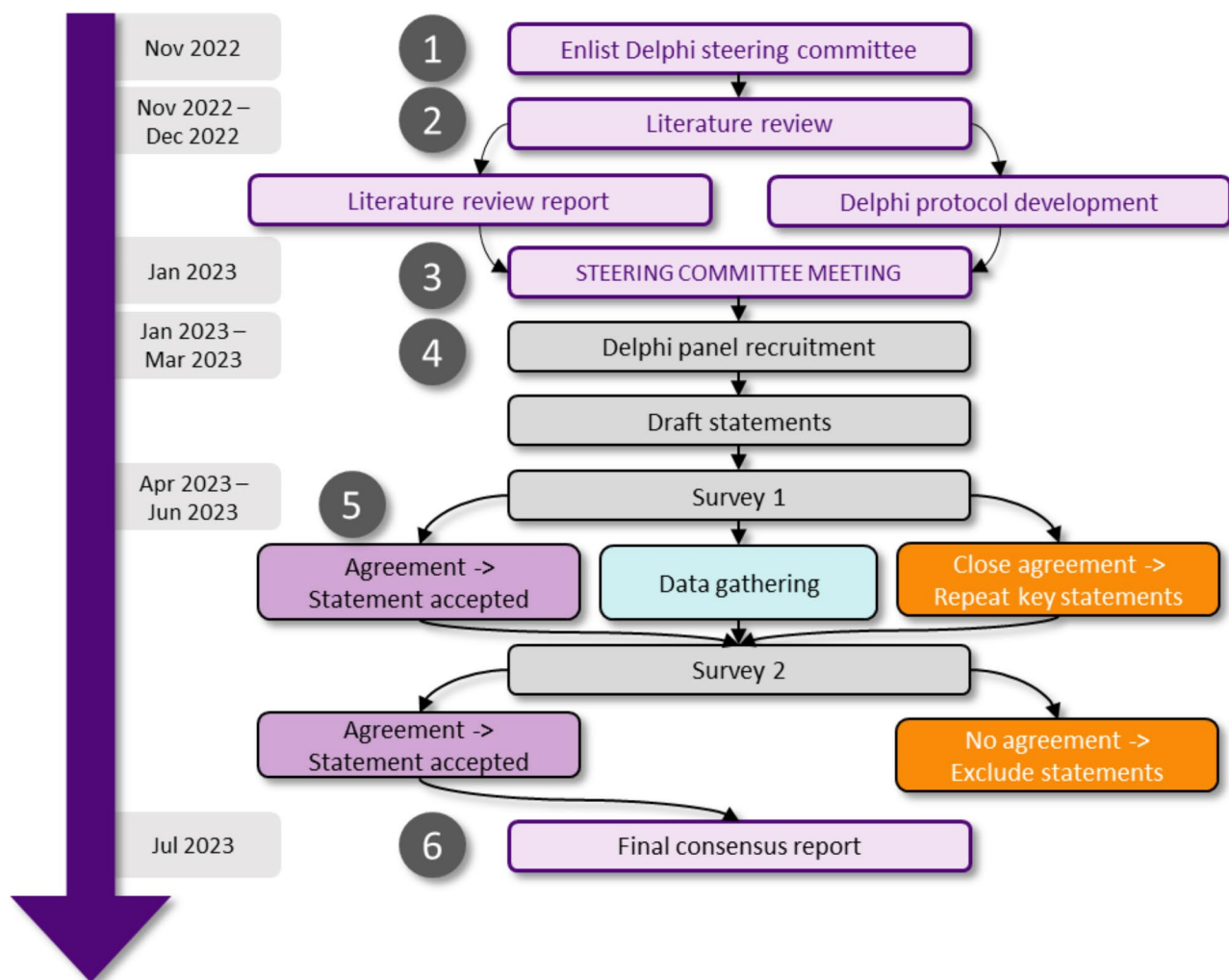
The aim of this study was, therefore, to investigate the level of expert consensus on optimal maternal nutrition during the early life course of the offspring, covering the critical preconception, pregnancy and lactation periods, using a modified Delphi method.

## Methods

### Study design

The study employed a modified Delphi process (Fig. 1), consisting of two iterative survey rounds, based on

published standards of Delphi methodology [38, 39]. First, the lead and corresponding authors (IC and RST), serving as co-chairs, identified experts to form a steering committee (SC). The SC consisted of eight clinicians and/or researchers specialising in gynaecology and obstetrics (IC, RD, FP), preconception epidemiology and medicine (RST), paediatrics (EI), nutrition (RO, LVR) and endocrinology (SP). To inform survey development and provide structure to SC discussions, a scoping review was conducted on 31 October and 1 November 2022, focusing on maternal nutrition, including diet and selected micronutrient needs during preconception and pregnancy, as well as existing guidelines for their intake and supplement use. We restricted the search to human studies that had been published in the last 5–10 years and in the English language. Details of the search strategy are included in the Supplementary Methods (Additional File 2). A total of 82 publications were reviewed in depth. Based on subsequent discussions of the literature review findings,



**Fig. 1** Overview of modified Delphi process

the SC prioritised topics for inclusion in the Delphi surveys, developed survey questions and determined the panel recruitment method along with the definition of consensus.

#### Panel recruitment

The corresponding and first authors of key articles identified in the literature review were invited to participate as expert panellists; 140 authors were invited to take part. No additional inclusion criteria were defined. Prior to participating, prospective panellists were informed of the survey topics and approximate survey length and told that their responses would be kept anonymous. Panellists did not receive reimbursement for their time. The SC were not panel members and did not complete the Delphi surveys. The study was reviewed by Pearl Institutional Review Board (2023-0047, <https://www.pearlirb.com/>) and received a Category 2 exemption from full review, in accordance with the US Department of Health and Human Services and Code of Federal Regulations (CFR; 45 CFR 46.104(d)(2)).

#### Delphi surveys

A two-round web-based survey was conducted between April and June 2023 using SurveyMonkey® (<https://uk.surveymonkey.com/>). All questions from both surveys are provided in the Supplementary Methods (Additional File 2). The first survey collected basic demographic information and was then organised into three main sections. Section 1 included multiple general questions relating to educational needs, existing guidelines, and approaches to diet (for example, a Mediterranean diet [40]) and supplement use. Section 2 was structured to correspond with the key periods of preconception, pregnancy and lactation. For each period, questions focused on the importance of supplementing with the following micro-nutrients for general or low-risk populations: folic acid, choline, iodine, magnesium, calcium, iron, selenium, DHA, and vitamins B1, B2, B6, B12, D and K. This was followed by a general subsection with questions around supplement use of specific nutrients. Section 3 included multiple general questions around tailored approaches and nutrient needs in specific at-risk groups.

Throughout the surveys, panellists were asked to rate questions on a 7-point Likert scale. For each question, a 'not applicable' (NA) option was included, and panellists were asked to select this if they felt that a question was outside of their experience or area of expertise. They were also encouraged to provide comments/reasoning for their responses in free-text boxes. Panellists' responses to the first survey were used to inform the focus of the second survey. In line with standard Delphi methodology [38, 39], which advocates for informed decision-making and result sharing, panellists received a summary of the

first survey's results prior to completing the second survey. For both surveys, panellists' responses were kept anonymous and were equally weighted.

#### Consensus definition and analysis

In line with other Delphi studies, consensus agreement/disagreement was defined a priori as  $\geq 75\%$  of panellists selecting 1 to 3 (agreement) or -1 to -3 (disagreement) for questions rated on a 7-point Likert scale [41]. 'NA' responses were considered invalid and excluded from the consensus calculation.

Questions on the importance of supplementing with specific nutrients that reached 'close consensus' in the first survey (defined as 70–74% of panellists selecting 1 to 3 or -1 to -3) were repeated in the second survey. To delve further into the rationale behind panellists' rating of importance, the second survey introduced additional questions on the strength of evidence that supplement use with each of the examined nutrients improves outcomes. In instances where panellists rated the evidence as weak, subsequent questions asked them to specify whether this was due to a lack of evidence, discrepancies in existing evidence, existing evidence being of low quality or other rationale. The strength of consensus was investigated using the median and interquartile range (IQR) once consensus had been reached. Consensus was considered strong if the median was  $\geq 2$  or  $\leq -2$  and the  $IQR \leq 1$ . Where relevant, free-text responses were described in the results. An overview of free-text responses is available upon request.

#### Results

In total, 140 experts were invited to participate in the panel. Of these, 35 (25%) participated in the first survey, with 32 completing and three partially completing the survey. Thirty-two (91%) panellists completed the second survey. Survey 1 ran from 28 March to 8 April 2023 and Survey 2 ran from 26 May to 13 June 2023. The panel (Maternal Nutrition Delphi Study Group) comprised 10 HCPs, 11 researchers and 14 joint HCP-researchers. Panellists were experienced in diverse clinical specialities, including gynaecology and obstetrics and nutrition. Demographic characteristics of the panellists are detailed in Table 1. Results from both surveys are provided in the Supplementary Results (Additional File 3).

#### General considerations around maternal nutrition

Panellists reached consensus on various aspects of maternal nutrition, encompassing educational needs, general approaches to diet and dietary supplement use, and perspectives on current guidelines (Additional File 3: Supplementary Results Table S1). There was strong consensus agreement on the importance of HCPs providing nutritional and supplement advice from preconception and

**Table 1** Demographic characteristics of panellists

Number of panellists	35
Continent	
Asia	2 (5.71%)
Australia	1 (2.86%)
Europe	25 (71.43%)
North America	6 (17.14%)
South America	1 (2.86%)
Current occupation	
Researcher/academic	11 (31.43%)
HCP	10 (28.57%)
Joint HCP-researcher/academic	14 (40.00%)
Clinical specialty	
Obstetrician/gynaecologist	4 (11.43%)
Nutritionist/dietician	10 (28.57%)
Paediatrician	4 (11.43%)
Endocrinologist	2 (5.71%)
Midwife	1 (2.86%)
Cardiologist	1 (2.86%)
Pharmacologist	1 (2.86%)
Biochemist	1 (2.86%)
Experience in current occupation	
≤ 5 years	0 (0%)
> 5–≤ 10 years	6 (17.14%)
> 10–≤ 15 years	8 (22.68%)
> 15–≤ 20 years	6 (17.14%)
> 20–≤ 25 years	6 (17.14%)
> 25 years	9 (25.71%)

HCP, healthcare professional

throughout lactation (combined estimates median = 2–3, IQR = 1, 97–100% agreement), as well as on the need for increased education and awareness in these areas for HCPs, pregnant people and the public (combined estimates median = 3, IQR = 1, 94–97% agreement).

Panellists strongly agreed on providing advice to follow a Mediterranean diet and regular national dietary guidelines (combined estimates median = 2, IQR = 1, 77–84% agreement).

There was no consensus on the Dietary Approaches to Stop Hypertension diet or that specific diets should not be advised. Both general multivitamin/multi-micronutrient supplement use and tailored individualised approaches were considered important (combined estimates median 2–3, IQR = 1, 79–88% agreement). In free-text comments, panellists noted that although individualised strategies are optimal, they are resource intensive and may not be economically viable or more effective at enhancing health or preventing additional complications in general populations.

Regarding current guidelines, there was consensus and close consensus that these are not clear or harmonised across countries and organisations, respectively (combined estimates median = -1, IQR = 1–2, 73–75% agreement).

### Micronutrient supplement use during preconception, pregnancy and lactation in general low-risk populations

Panellists reached consensus on the importance of supplement use, and on the strength of evidence that supplement use improves outcomes and/or foetal development, for some key micronutrients across different stages of pregnancy (Figs. 2 and 3; Additional File 3: Supplementary Results Tables S2–S7).

#### Preconception

For a person trying to conceive, panellists strongly agreed that supplement use should be advised up to 6 months before they get pregnant (combined estimates median = 2, IQR = 1, 84% agreement). There was consensus that a balanced diet is mostly not sufficient to meet all micronutrient requirements and that supplement use should be advised (76% agreement, median = -1, IQR = 1).

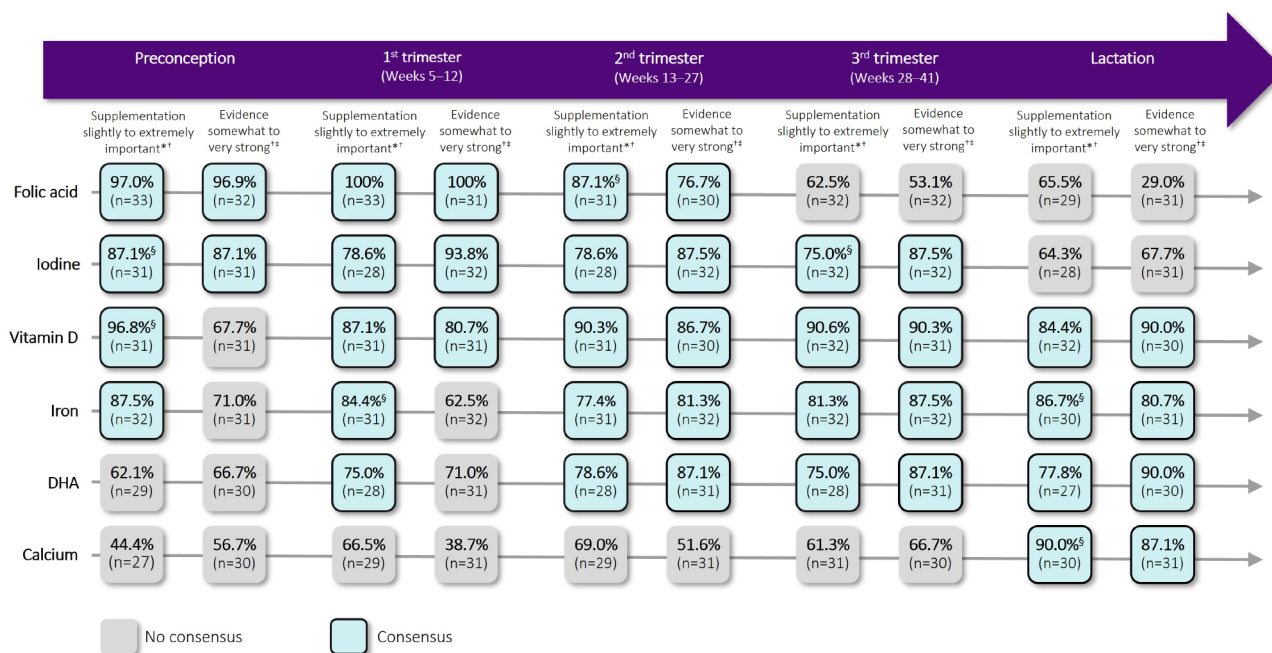
In the preconception period, panellists strongly agreed on the importance of supplementing with vitamin D, folic acid, iodine and iron (combined estimates median = 2–3, IQR = 0–1, 87–97% agreement). They also agreed that the evidence for supplementing with folic acid and iodine is somewhat to very strong during this phase (combined estimates median = 1–3, IQR = 1, 87–97% agreement). Although not reaching consensus, most panellists considered the evidence for supplementing with vitamin K during preconception to be somewhat to very weak (62% agreement, median = -1.5, IQR = 2), attributing this primarily to a lack of evidence.

#### First trimester

For people in the first trimester, consensus was reached on the importance of supplementing with vitamin D, folic acid, iodine, iron and DHA (combined estimates median = 2–3, IQR = 1–1.5, 75–100% agreement). Panellists also agreed that the evidence for supplementing with vitamin D, folic acid and iodine during this stage is somewhat to very strong (combined estimates median = 2–3, IQR = 1–2, 81–100% agreement). Despite not reaching consensus, the majority of panellists regarded the evidence for supplementing with vitamins B2 and K to be somewhat to very weak (combined estimates median = -1, IQR = 2, 52–62% agreement), with most ascribing this to a lack of evidence.

#### Second trimester

For the second trimester, there was consensus agreement on the importance of supplementing with the same nutrients as for the first trimester: vitamin D, folic acid, iodine, iron and DHA (combined estimates median = 2, IQR = 1–2, 77–90% agreement). Consensus was also reached that the strength of evidence for supplementing with each of these nutrients during the second trimester is somewhat to very strong (combined estimates



**Fig. 2** Micro- and macro-nutrients for which consensus was reached on supplement use. \*Percentages represent the proportion of panellists selecting 1–3 on a 7-point Likert scale of importance for questions on the importance of supplement use. †n refers to the number of valid responses; ‘NA/unsure’ responses were considered invalid and excluded. ‡Percentages represent the proportion of panellists selecting 1–3 on a 7-point Likert scale of strength for questions on the strength of evidence that supplement use improves outcomes and/or foetal development. §Based on data from Survey 2; questions reaching close consensus in Survey 1 were repeated in Survey 2. DHA, docosahexaenoic acid

median = 1–2, IQR = 1–2, 77–88% agreement). Although not reaching consensus, most panellists considered the evidence for supplementing with vitamins B2 and K during the second trimester to be somewhat to very weak (combined estimates median = -1–1.5, IQR = 2, 52–58% agreement), primarily due to a lack of evidence.

### Third trimester

In the third trimester, panellists reached consensus on the importance of supplementing with vitamin D, iodine, iron and DHA (combined estimates median = 2, IQR = 1–1.5, 75–91% agreement). There was also consensus that the strength of evidence for supplementing with each of these nutrients at this stage is somewhat to very strong (combined estimates median = 1–2, IQR = 1–1.3, 87–90% agreement). Despite not reaching consensus, most panellists rated the evidence for supplementing with selenium and vitamins B1, B2 and K during the third trimester to be somewhat to very weak (combined estimates median = -1, IQR = 2–3, 52–57% agreement), mainly ascribing this to a lack of evidence.

### Postpartum/lactation

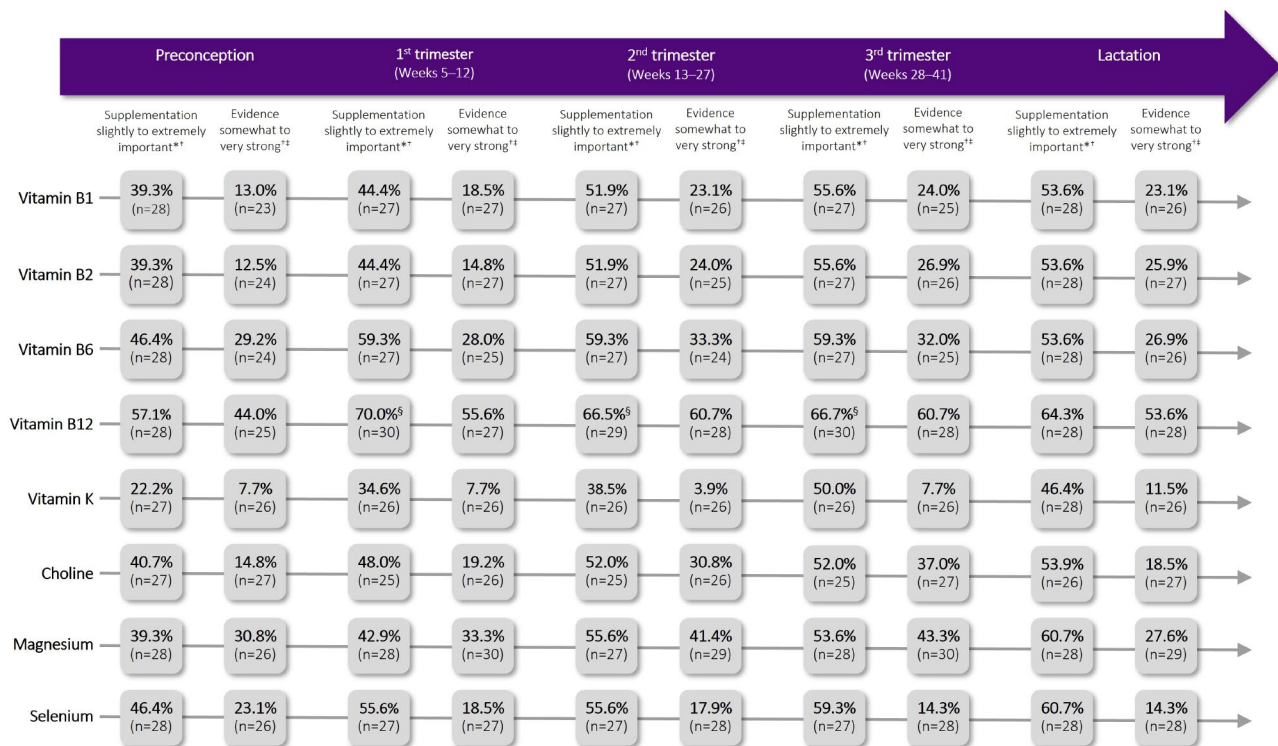
During lactation, there was consensus agreement on the importance of supplementing with vitamin D, iron, DHA and calcium (combined estimates median = 1–2, IQR = 1, 78–90% agreement). Panellists also agreed that the strength of evidence for supplementing with each of these

nutrients in this phase is somewhat to very strong (combined estimates median = 1–2, IQR = 1, 81–90% agreement). While there was no consensus on the strength of evidence for other micronutrients, the majority of panellists regarded the evidence for supplementing with choline, selenium and vitamins B1, B2, B6 and K during lactation to be somewhat to very weak, with most again attributing this to a lack of evidence (combined estimates median = -1, IQR = 2–3, 52–62% agreement). There was no consensus on whether people should be advised to continue supplement use post-weaning or if people who are not breastfeeding should continue postpartum.

### Approaches to nutrition in specific at-risk groups during pregnancy

Panellists reached consensus on the need to tailor dietary supplement use recommendations to a person’s lifestyle, medical conditions and nutrition-related pregnancy complications (combined estimates median = 2–3, IQR = 1–2, 88–100% agreement; Additional File 3: Supplementary Results Table S8). There was strong consensus that dietary supplement use recommendations are not universally applicable (84% agreement, median = -2, IQR = 1).

Although there were a relatively high number of ‘NA’ responses to questions in this section, panellists agreed that approaches to diet and dietary supplement use during pregnancy should be tailored for each of the examined groups, including athletes/highly active people,



**Fig. 3** Micro- and macro-nutrients for which consensus was not reached on supplement use. \*Percentages represent the proportion of panellists selecting 1–3 on a 7-point Likert scale of importance for questions on the importance of supplement use. †n refers to the number of valid responses; †NA/unsure responses were considered invalid and excluded. ‡Percentages represent the proportion of panellists selecting 1–3 on a 7-point Likert scale of strength for questions on the strength of evidence that supplement use improves outcomes and/or foetal development. §Based on data from Survey 2; questions reaching close consensus in Survey 1 were repeated in Survey 2

people following vegan/vegetarian diets, restricted diets due to food intolerance, obesity, polycystic ovary disease (PCOS), diabetes mellitus and/or a history of birth complications such as NTDs, pre-eclampsia, PTB or gestational diabetes (combined estimates median = 2–3, IQR = 0–1, 86–100% agreement). In free-text comments, panellists noted the need to consider a person's biomarkers, nutritional status and the nature of any disease/complications. In each of the examined groups, there was consensus agreement on the importance of adjusting supplement recommendations for vitamin D, iron and DHA (Additional file 3: Supplementary Results Table S7). For other nutrients, ratings of importance varied considerably between the groups.

## Discussion

This Delphi study examined the level of expert consensus on optimal maternal nutrition including diet and micronutrient supplement use. An international multidisciplinary panel, with expertise in specialties such as nutrition, gynaecology and obstetrics, participated and reached consensus in key areas of uncertainty, including general considerations around diet and dietary supplement use, the importance of supplementing with folic acid, DHA, iron, iodine, calcium and vitamin D

during distinct phases of preconception, pregnancy and lactation, and the at-risk groups requiring tailored approaches.

Evidence suggests that micronutrient intake is generally lower than recommended, even in high-income countries [42, 43]. Examples of shortfalls at the population level in achieving recommended levels have been reported for vitamin D [35, 44], folate [45–47], iodine [30, 47, 48], vitamin B12 [49, 50], iron [47] and DHA [51], which can be particularly difficult to achieve via diet during pregnancy and lactation, when some fish species should be avoided due to heavy metal content [30, 52, 53].

Among the key general insights, panellists strongly agreed on providing advice to follow a Mediterranean diet, in line with several studies demonstrating that a maternal healthy diet and lifestyle contribute to improving short- and long-term reproductive and pregnancy outcomes [54–56]. The Mediterranean diet can be a good source of folate, DHA, vitamin D and other vitamins, as it emphasises foods that are rich in antioxidants, vitamins, minerals, polyphenols and fibre, i.e. vegetables, fruits, grains, nuts, olive oil, fish and seafood, and white meat [40]. Adherence to the Mediterranean diet during pregnancy has been shown to be advantageous, especially with regard to reducing the risk of gestational diabetes

and gestational weight gain [57]. However, it is not clear which component(s) of the diet these positive effects might be attributed to, and barriers to adoption exist in countries with limited access to the types of foods necessary for this diet.

However, panellists also agreed on the lack of clarity and consistency in current guidelines, and the need for education in these areas for HCPs, pregnant people and the public. These findings align well with previous surveys of gynaecologists in which uncertainty around micronutrient supplement use during pregnancy was emphasised, along with the lack of widely recognised guidelines for gynaecologists [7, 58]. Altogether, this highlights the need for standardised, clear guidelines to ensure consistent and evidence-based recommendations.

### **Consensus findings for micronutrient supplement use in pregnancy and lactation in general (low-risk) populations**

#### **Folate**

There was strong consensus for folic acid supplement use during the preconception period and the first trimester, which is in line with existing guidelines to take supplemental folic acid (vitamin B9) to reduce the risk of NTDs. Obstetricians and gynaecologists are generally aware of the importance of folic acid intake during preconception and the first trimester, but may be less aware of the role of folic acid in prevention of other congenital defects [59] as a substrate in one-carbon metabolism [58, 60–62]. In addition, folic acid supplement use during early pregnancy (4 weeks before to 8 weeks after conception) appears to benefit neurocognitive development of the child [63]. However, the potential advantages of folic acid supplement use beyond the first trimester are unclear. A recent systematic review and meta-analysis (three randomised controlled trials [RCTs] and 17 cohort studies) has shown that folic acid supplement use during pregnancy was associated with a lower risk of pre-eclampsia, although the timing of supplement use was not specified [64]. Folic acid supplement use after the first trimester has been shown to increase maternal and cord blood folate levels and prevent the increase in homocysteine normally seen late in the second and third trimesters [65, 66]. However, given that these studies did not include pregnancy outcomes and that current guidelines only cover preconception and early pregnancy, the lack of consensus for folic acid during the third trimester may be expected.

#### **Other B vitamins**

Consensus for other B vitamins (B1, B2, B6, B12) besides folic acid was weak. Similar to folate, vitamins B2, B6 and B12 are involved as cofactors in one-carbon metabolism and are therefore likely to be relevant for foetal development [67]. For example, studies have shown that using

multivitamin supplements containing folic acid and iron in addition to other nutrients (vitamins B1, B2, B3, B6, B12, vitamins A, D, E, omega-3 fatty acids and minerals) was more likely to show a positive impact on pregnancy outcomes than those containing only folic acid and iron [67]. Using multi-micronutrients including folic acid and iron could be of special importance among women from low- and middle-income countries where multiple micronutrient deficiencies are common [67]. Vitamin B12 supplement use during pregnancy could lower the risk of deficiency in the mother during pregnancy and lactation [68]. The evidence on pregnancy outcomes such as PTB and low birth weight is uncertain due to the low number of studies available [68]. Unrecognised vitamin B12 deficiency in the mother is a risk factor for vitamin B12 deficiency in newborns, which can manifest in infants at age 3–6 months as serious developmental delay and neurological symptoms. A German pilot study of newborns reported a prevalence rate for vitamin B12 deficiency of 1:3586 births (95% confidence interval 1:3577–1:3596) [69]. If antenatal supplements contain the adequate dose of vitamin B12, this deficiency could be prevented in mothers and neonates. Thus far, methodological limitations prevent definitive conclusions on specific clinical outcomes related to each of the B vitamins [68]. This could explain why B vitamins (other than folic acid) are not yet embedded in current guidelines, and the weak to no consensus for B vitamins in this Delphi.

#### **DHA**

There was consensus agreement on the importance of supplementing with DHA across all three trimesters of pregnancy and throughout the lactation period. Interestingly, when voting on the strength of evidence that DHA supplement use improves pregnancy outcomes and/or foetal/neonatal development, a consensus of  $\geq 75\%$  was reached for the second and third trimesters and lactation, but not for the first trimester.

DHA/omega-3 fatty acid supplement use in pregnancy has been shown to reduce risk of PTB and early preterm birth (EPB). A recent Cochrane review found an 11% risk reduction of PTB < 37 weeks, and a 42% risk reduction of EPB < 34 weeks [20], but in most studies supplement use only started in the second trimester, around 20 weeks of gestation. A recent clinical practice guideline based on a review of the available evidence and a formal consensus process advocates DHA and eicosapentaenoic acid supplement use in pregnancy for risk reduction of PTB and EPB [70].

Positive effects of DHA/omega-3 long-chain polyunsaturated fatty acids on pregnancy outcomes are likely driven by the downregulation of inflammation, mediated by changing the balance between pro- and anti-inflammatory prostaglandins in the uterus [71]. Moreover, the

accumulation of DHA in the brain in the third trimester and first year of life may have positive effects on brain and cognitive development [72].

### **Iron**

There was consensus agreement on the importance of iron supplement use in both general (low-) and high-risk populations across all stages of female reproduction, with consensus agreement on the improvement of pregnancy, foetal and neonatal outcomes for the second and third trimesters, and lactation period. Iron-deficient anaemia is highly prevalent worldwide, with frequencies of iron deficiency ranging from 40% in early pregnancy to 80% in late pregnancy [73, 74]. This explains the consensus and awareness among experts on the need for iron supplement use from preconception to the postpartum period. Iron is essential for foetal neurogenesis and placental development, as well as haematopoiesis in mother and foetus. An increase in severe maternal morbidity and mortality [75], as well as increased risks of short- (i.e. PTB, small for gestational-age babies) and long-term (i.e. autism spectrum disorders, impaired cognitive status) adverse outcomes in the offspring [76], were described in iron-deficient anaemic pregnant women, although benefits of routine antenatal supplement use are controversial. Nevertheless, routine screening for anaemia and iron deficiency in early pregnancy and the third trimester is consistently supported as cost-effective [26, 77].

### **Iodine**

The panel reached consensus agreement on the importance of iodine supplement use from preconception through all stages of pregnancy, also reaching consensus on the strength of the evidence. Pregnant women and infants are exceptionally vulnerable to iodine deficiency; poor iodine intake has been shown to cause harmful effects on the foetus, including delayed development and brain maturation [78]. Adequate iodine supplement use from preconception until the end of the first trimester of pregnancy has been shown to reduce the incidence of cretinism in the areas of highest deficiency risk by up to 73% [79, 80]. The need for iodine supplement use during pregnancy was also emphasised in a survey of German gynaecologists [7]. However, a recent Cochrane review did not find significant benefits of iodine supplement use in the preconception, pregnancy or postpartum periods, although these findings must be interpreted cautiously due to limited data and low-quality trials [81]. The widespread problem of iodine deficiency has led medical societies in Europe and North America to recommend that women planning a pregnancy, or who are pregnant or breastfeeding, take a daily tablet containing at least 150 µg of iodine [82].

### **Calcium**

The importance of optimal calcium intake is seen during periods of rapid foetal growth, particularly the third trimester. Physiological adaptations with increased intestinal mineral absorption during pregnancy ensure maternal bone integrity, mineralisation of the foetal skeleton and continued skeletal growth in the neonate/infant [83]. Therefore, healthy pregnant people residing in countries where calcium intake is generally higher may not benefit from supplement use compared with women in countries where the calcium intake is low. It is possible that calcium was not specifically considered in a survey of German gynaecologists due to likely high milk intake in the population [7]. The lack of consistency in current guidelines may have led to distinctions in expert opinion on calcium supplement use during pregnancy in the present study with its focus on a European population. By contrast, during lactation, when calcium supply to breast milk is mainly derived from the skeleton of the mother [83], consensus was reached on calcium supplement use.

Beyond maintaining calcium homeostasis, a Cochrane review has linked calcium supplement use to lowering of blood pressure and prevention of pregnancy-induced hypertension and related complications [84]. However, the impact of supplement use on the risk of preterm delivery remains conflicted, as does the quality of evidence for outcomes other than hypertensive disorders. Consequently, current WHO recommendations are confined to at-risk situations [85].

### **Vitamin D**

There was consensus agreement on the importance of vitamin D supplement use in the preconception phase, across all three trimesters of pregnancy and throughout the lactation period. In agreement with these recommendations, the strength/quality of evidence arguing for vitamin D supplement use to improve maternal and/or foetal/infant health was also rated as somewhat to very strong, except for the preconception period. This strong consensus in favour of widespread vitamin D supplement use may not sufficiently reflect the still ongoing scientific discussion on vitamin D in these settings [86–88]. There is compelling evidence that a poor vitamin D status, reflected by low serum 25(OH)D concentrations, is associated with various adverse pregnancy outcomes [86]. In contrast, data from vitamin D RCTs are inconsistent and often limited due to low sample sizes, enrolment starting after the first trimester, and/or including women with a sufficient vitamin D status [87, 88]. While it is beyond the scope of this manuscript to critically appraise the whole literature on vitamin D, widespread vitamin D supplement use is supported by evidence that (a) vitamin D deficiency is very common, (b) vitamin D is critical for bone health (i.e. prevention and treatment of rickets and

osteomalacia) as consistently documented by evidence-based guidelines, and (c) vitamin D supplement use at moderate doses (e.g. 800–2000 IU, 20–50 µg daily) is relatively safe from preconception throughout pregnancy until lactation [86, 89]. There are also additional potential beneficial effects of vitamin D, such as for fertility, preventing pre-eclampsia or gestational diabetes mellitus, although evidence remains limited [86, 87, 90].

### **Choline**

Choline supplement use in pregnancy and lactation did not achieve consensus among the panellists. Choline contributes to normal liver function and lipid metabolism in adults [91, 92]. The requirements for choline are greater during pregnancy and lactation than outside these critical time periods [91, 92], due to the need to meet the needs of both the mother and foetus or breastfed infant at the same time. Choline is actively transported through the placenta and accumulates in the foetus. Choline supplement use by the mother leads to higher choline levels in breast milk and consequently increased choline intake for breastfed infants [93]. The EFSA has recently evaluated the evidence on the role of maternal choline intake in health outcomes in the foetus and infants [94], and concluded that a sufficient intake of choline during pregnancy and lactation (480 mg/day and 520 mg/day, respectively) can contribute to normal liver function of the foetus and exclusively breastfed infants [94].

A recent meta-analysis of observational studies reported that low maternal choline intake or blood levels are associated with a higher risk of NTDs in newborns [18]. Higher choline intake is likely to have positive impacts on foetal brain development and neurodevelopment of the child after birth [18]. The growing evidence on the role of choline during pregnancy and lactation is still awaiting translation into population-wide recommendations and policy. This could explain why the panellists did not prioritise choline supplement use for pregnant and lactating people in this Delphi study.

### **Other examined micronutrients: Vitamin K**

Consensus among panellists was that the evidence for vitamin K supplement use was weak. This reflects the current lack of evidence, with most pregnancy and neonatal outcomes unassessed, not significant or providing very low-quality evidence, and few trials reporting neonatal adverse effects. A study of women admitted for elective caesarean section found that vitamin K supplement use was favourable for maternal bleeding but was of limited value for neonatal bleeding and other outcomes [95]. The existing literature gaps

warrant future investigations on un-assessed or inadequately reported outcomes [96].

### **Consensus findings for specific at-risk groups**

People following vegan/vegetarian diets, restricted diets, or with obesity, PCOS, diabetes or a history of pregnancy complications were identified by panellists as groups for whom supplement use advice should be tailored.

Particularly, the global “diabesity” pandemic involves a growing number of women of reproductive age and is associated with increased risk for PCOS and infertility, gestational diabetes, and other pregnancy and birth complications [97]. Also, a recent systematic review revealed that maternal obesity increases the risk for nutritional deficiencies, especially folate, vitamin D and vitamin B12 [98]. Hence the panellists’ concern that tailored recommendations for people living with obesity and planning pregnancy should be developed. For women with a history of bariatric surgery, a well-recognised high-risk group for nutritional deficiencies [99], evidence-based guidelines have recently been developed [100]. Of note, panellists emphasised the need for more research on dietary/nutritional requirements in these specific at-risk groups. Ethical concerns around allocating specific at-risk groups of pregnant people to placebo arms in large micronutrient RCTs may, however, limit our ability to clarify several remaining knowledge gaps during preconception and pregnancy in the future.

### **Limitations**

While the Delphi method is recognised as reliable and robust, it is not without limitations, including the lack of standardised criteria for defining consensus and the possibility that anonymity may lead to insufficiently considered responses. Additionally, in the present study, it is possible that the broad scope of the Delphi surveys, spanning different areas of expertise and employing equal weighting of responses, influenced consensus and contributed to the high prevalence of ‘NA’ responses for certain questions. Although there was representation from a range of specialties, the panel selection method may have resulted in panellists with narrow expertise and contributed to the observed variability in responses. The possible bias towards the northern hemisphere and developed countries may also have impacted the generalisability of the findings. Another limitation is that we did not specifically account for between-country differences in diet and food fortification.

### **Future directions**

Future research is needed to address the evidence gaps highlighted by the Delphi findings, which confirmed

strong evidence for maternal supplement use of some micronutrients, yet consistently pointed to a lack or low level of evidence for others. The variability in panel responses and lack of consensus around micronutrients such as choline and vitamin B12, despite accumulating evidence of their benefit, may suggest knowledge gaps among HCPs. This reinforces the importance of developing targeted educational programmes for those involved in maternal care, care of people planning or preparing to become pregnant, and creating accessible lay communications for the public. Alongside educational efforts, there is a pressing need for harmonised supplement use guidelines that reflect the latest evidence. The generalisability of results must be addressed, with studies needed in different populations and research ideally led by an international consortium. Nutritional research is, in general, complicated: as people eat diets and not nutrients, it is difficult to study the effect of a single nutrient on a study participant in a supplement study, because we might miss the interaction with other nutrients. Therefore, we would suggest conducting studies in populations with deficiencies of selected micronutrients, for example to better characterise the role of adequate vitamin B12 in pregnancy and birth outcomes for women following vegan diets. It is also important to study the long-term effects on offspring health in populations where nutritional data have been collected during pregnancy. The development of harmonised supplement use guidelines is more relevant than ever, both for women and for healthcare providers, and scientific societies and institutions need to be involved to reach consensus on guidelines. Nutrient and supplement guidelines should balance general and personalised approaches, as well as considering the toxicity of high dosages and cost-effectiveness for low- or general-risk populations.

Similar Delphi approaches could prove valuable in exploring areas of consensus, as well as evidence and knowledge gaps in the field of nutraceuticals, in particular approaches to pre-, pro-, syn- and postbiotics.

## Conclusions

This Delphi study revealed robust consensus on various aspects of maternal nutrition, including the need for education/awareness around maternal diet and dietary supplement use, the lack of clarity and consistency in current guidelines, the importance of supplementing with folic acid, vitamin D, iron, iodine, DHA and calcium during preconception and across specific phases of pregnancy, and the at-risk groups requiring tailored approaches. The lack of consensus around several other micronutrients, despite growing evidence of their benefit, reinforces the need for prompt

translation of available evidence into guidelines, policies and practice. Future initiatives are required to facilitate the development of harmonised supplement use guidelines that reflect the latest evidence and to enhance maternal nutrition education in order to improve the health of at least two generations.

## Abbreviations

BfR	German Federal Institute of Risk Assessment
CFR	Code of Federal Regulations
D–A–CH	(Germany, Austria, Switzerland)
DHA	Docosahexaenoic acid
EFSA	European Food Safety Authority
EPB	Early preterm birth
HCP	Healthcare professional
IOM	US Institute of Medicine
IQR	Interquartile range
IU	International units
NA	Not applicable
NTD	Neural tube defect
PCOS	Polycystic ovary disease
PTB	Preterm birth
RCT	Randomised controlled trial
RDI	Recommended dietary intake
SACN	Standing Advisory Committee on Nutrition
SC	Steering committee
UNICEF	United Nations Children's Fund
WHO	World Health Organization

## Supplementary Information

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Supplementary Material 1: Additional File 1

Supplementary Material 2: Additional File 2

Supplementary Material 3: Additional File 3

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## Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). IC, RD, EI, RO, FP, SP, LR and RST were all involved in the study design, data analysis and interpretation, reviewed and revised drafts of the manuscript and approved the final draft. The 'Maternal Nutrition Delphi Study Group' participated in the study as expert panellists.

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#### Data availability

All data generated or analysed during this study are included in this published article (and its supplementary information files) – and an overview of the free-text comments is available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

The study was reviewed by Pearl Institutional Review Board (2023-0047, <https://www.pearlirb.com/>) and received a Category 2 exemption from full review, in accordance with the US Department of Health and Human Services and Code of Federal Regulations (CFR; 45 CFR 46.104(d)(2)). Participants gave informed consent to participate as part of the survey and could withdraw at any time.

##### Consent for publication

Not applicable.

##### Competing interests

IC has received payments/honoraria unrelated to the present publication from Procter & Gamble (P&G), Bayer and Italfarmaco and has participated on a data safety monitoring board/advisory board for Italfarmaco. RD has received payments/honoraria unrelated to the present publication from P&G and Metagenics and participated on a data safety monitoring board/advisory board for Pfizer and Janssen Pharmaceuticals. RO and SP have received consulting fees and payments/honoraria unrelated to the present publication from P&G. All authors received payment for participation in a steering committee meeting related to the data presented in this manuscript.

##### Author details

- <sup>1</sup>Department of Women, Mother and Neonate, "Vittore Buzzi" Children's Hospital, University of Milan, Milan, Italy
- <sup>2</sup>Department of Obstetrics and Gynaecology, University Hospitals Leuven, Leuven, Belgium
- <sup>3</sup>Department of Obstetrics, Gynaecology and Fertility, GZA campus Sint-Augustinus, Wilrijk, Belgium
- <sup>4</sup>Department of Pediatrics, University of Turku, Turku University Hospital, Turku, Finland
- <sup>5</sup>Department of Clinical Chemistry, Saarland University Hospital, Homburg, Germany
- <sup>6</sup>Department of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria
- <sup>7</sup>Department of Obstetrics and Gynaecology, Erasmus MC, University Medical Center Rotterdam, Dr. Molewaterplein 40, Rotterdam 3015 CE, Netherlands
- <sup>8</sup>Present address: Department of BioMedical and Clinical Sciences, University of Milan and Fondazione IRCCS CA'GRANDA, Ospedale Maggiore Policlinico, Milan, Italy
- <sup>9</sup>Present address: Division of Human Nutrition and Health, Wageningen University, Wageningen, Netherlands

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