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Abbreviated Class Review: Prenatal Vitamins

Month/Year of Review: November 2014 **End date of literature search:** September 2014
PDL Class: None

Research Questions:

- Is there evidence to support and cover the use of specific products with good value?
- Are certain reformulations of prenatal vitamins more effective than safer than individual components or other formulations?
- Are there subpopulations that certain vitamins are more effective or safer than others?
- Is there evidence that supplementation improves clinical outcomes?

Conclusions:

- There is high quality evidence that folic acid supplementation (alone or in combination with other vitamins and minerals) is effective in preventing neural tube defects compared with placebo (RR 0.28; 95% CI 0.15 to 0.52).[1]
- There is moderate quality evidence that prenatal supplementation with daily iron reduces the risk of low birthweight (RR 0.81; 95% CI 0.68 to 0.97) and prevents maternal anemia (RR 0.30; 95% CI 0.19 to 0.46) and iron deficiency (RR 0.43; 95% CI 0.27 to 0.66) during pregnancy.
- In settings of low calcium dietary intake, 1.5 to 2.0 g of elemental calcium per day is recommended in pregnant women.
- Well-nourished women may not need a multivitamin or prenatal vitamin and there is insufficient evidence of any benefit with universal supplementation. However, in the absence of a careful evaluation by a nutritionist, it is reasonable to recommend them. Often, the convenient way to get iron and folic acid is to take a daily multivitamin containing adequate amounts of both.
- There is no evidence of any difference between formulations of prenatal vitamins. An adequate prenatal vitamin should include 400 to 800 micrograms of folic acid and 30 mg of iron.

Recommendations:

- Include Prenatal Vitamins on the PDL and make all legend products preferred on the PDL to ensure high quality products with adequate amounts of folic acid are promoted.

Reason for Review:

The multivitamins and antioxidant multivitamins, and electrolytes were reviewed for clinical efficacy/effectiveness and safety. Prior authorization was proposed for multivitamins and antioxidant multivitamin supplements to approve for documented nutritional deficiency or diagnosis associated with nutritional deficiency. For mono vitamin supplements and electrolytes, including calcium, vitamin D, folic acid, vitamin B, the ferrous salt formulations, potassium, magnesium, and phosphate, specific agents were listed as preferred and non-preferred based on cost comparisons when no clinical advantage was identified. The additional minerals, electrolytes, and vitamins will be reviewed similarly.

Background:

Complementary and alternative medicine refers to preventive and therapeutic modalities not considered to be part of conventional medicine.[2] This includes dietary supplements and has increased dramatically in North America recently in general populations, as well as CVD populations. Evidence of both benefits and harms of adding supplements to medical treatments has been reported, and there remains debate concerning the efficacy and safety of dietary supplements [3] Safety concerns include the potential adverse effects, contamination of preparations, and mislabeling. Dietary supplements are regulated with much less rigor than prescription medications.[4] While randomized controlled trials are the gold standard for evidence based medicine, data on the efficacy and safety of dietary supplements is lacking, insufficient, or inconsistent. There is also a paucity of standardized guidelines for the use of these products. Even if there is guidance and/or evidence that a particular vitamin or dietary supplement may benefit patients, the question of which manufacturer or product to recommend is also raised. There are quality assessment programs available to ensure the quality of these products. This includes consumerlab.com, NSF International, and US pharmacopeia. Currently there are no specific vitamin policies under the Oregon Health Plan. A multivitamin with folic acid is included in the prevention table for pregnant patients.

Nutrient deficiencies are a public health concern in many countries in the world. RCTs in children in developing nations have shown that vitamin A supplementation decreases morbidity and all-cause mortality. However, the benefit of these supplements in nonpregnant adults in the US and other Western nations is less clear.[5] Malnutrition is both a cause and effect of poor health.[6] Factors contributing to disease related malnutrition include impaired intake (confusion, medication, poor appetite), impaired digestion and/or absorption (medical and surgical problems effecting the stomach, intestine, pancreas, and liver), altered requirements (increased metabolic demands), excess losses (vomiting, diarrhea, fistulae, stomas, burns). The National Institute for Health and Clinical Excellence recommends that all patients who have malnutrition due to one of the above reasons, in addition to sufficient calories, protein, and fluids, receive adequate electrolytes, minerals, micronutrients, and fiber if appropriate. [6] However, their evidence review found no data to support the routine use of vitamin and mineral supplements in either acute hospitalized patients or older residents in nursing homes. They recommend that if there is a concern about adequate micronutrient intake, a complete oral multivitamin and mineral supplement providing the reference nutrient intake should be considered by healthcare professionals.

Prenatal vitamins generally contain a variety of vitamins and minerals and are often similar to multivitamins used outside of pregnancy, with some differences. Prenatal vitamins typically contain more folic acid and iron than do standard adult multivitamins. Some vitamins come from strong evidence, including folic acid. Periconceptional folic acid supplementation is recommended since there is strong evidence that it reduces the risk of neural tube defects. Approximately 41.8% of pregnant women worldwide are anemic.[7] Iron has been shown to support the baby's growth and development and supplementation with iron is recommended in the United States. But for most vitamins, data are limited and there is insufficient evidence supporting preventive supplementation with vitamin and mineral supplements outside of folic acid.[8] Multivitamin supplements are recommended for pregnant women who cannot meet the recommended intake through food intake and are especially beneficial for women in developing countries.[9]

Methods:
A Medline literature search ending September 2014 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) for prenatal vitamins and nutrition during pregnancy was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A Cochrane Collaboration systematic review evaluated the effectiveness and safety of any vitamin supplementation on the risk of spontaneous miscarriage, maternal adverse outcomes and fetal and infant adverse outcomes.[10] Studies included vitamin A, alone or with iron, folic acid, zinc or multivitamins. Overall, no significant differences were observed between women taking vitamins compared to control for total fetal loss (RR 1.04; 95% CI 0.95 to 1.14), early or late miscarriage (RR 1.09; 95% CI 0.95 to 1.25) or stillbirth (RR 0.86; 95% CI 0.65 to 1.13). Women on vitamins were more likely to have a multiple pregnancy (RR 1.38; 95% CI 1.12 to 1.70).

The Cochrane Collaboration reviewed the effects of periconceptional supplementation with folic acid to reduce neural tube defects.[1] A total of 5 randomized controlled trials (n=6105) were included in the systematic review. In all trials, supplementation started before pregnancy and discontinued after 12 weeks of pregnancy. However, the doses varied from less than 360 mcg to 4000 mcg daily. Of the 6105 women, 1949 had a history of neural tube defects and 4156 did not. All of the studies were published before 2001 and had an unclear or low risk of bias. Overall, the results are consistent in showing a protective effect of daily folic acid supplementation (alone or in combination with other vitamins and minerals) in preventing neural tube defects compared with placebo (RR 0.28; 95% CI 0.15 to 0.52). Four trials included women with a history of neural tube defects and folic acid supplementation reduced the recurrence of a pregnancy affected by another defect (RR 0.32; 95% CI 0.17 to 0.60). Four of the trials included folic acid with other micronutrients compared with micronutrients without folic acid and also showed a significant difference in favor of those receiving folic acid supplementation (RR 0.29; 95% CI 0.15 to 0.56). There was no statistically significant difference in any effects on prevention of other birth defects, including cleft palate, cleft lip, congenital cardiovascular defects, and miscarriages.

A third systematic review from the Cochrane Collaboration evaluated multiple-micronutrient supplementation (MMS) for women in developing countries during pregnancy.[11] Results from 21 trials demonstrated that compared with iron and folate supplementation, no supplementation, or placebo MMS resulted in a statistically significant decrease in the number of low birth weight babies (RR 0.89; 95% CI 0.83 to 0.94) and small for gestational age (SGA) babies (RR 0.87; 95% CI 0.81 to 0.95). No differences were seen in preterm births, miscarriage, maternal mortality, perinatal mortality, stillbirths and neonatal mortality. There was insufficient data to assess neural tube defects, neurodevelopmental delay, cost of supplementation, side-effects of supplements, maternal well being or nutritional status of children. The authors concluded that although a benefit in low birthweight outcomes was seen, more evidence is needed to replace the recommendation of routine iron and folate supplementation with multiple micronutrients.

A high quality systematic review assessed daily oral iron supplementation during pregnancy.[12] Forty three studies were included in the meta-analysis, and the

daily dose of elemental iron ranged from 9-90 mg in trials. Overall, women taking oral supplementation were less likely to have low birthweight newborns compared with no iron (RR 0.81; 95% CI 0.68 to 0.97; based on 11 trials). Iron supplementation reduces the risk of maternal anemia at term (RR 0.30; 95% CI 0.19 to 0.46) and iron deficiency (RR 0.43; 95% CI 0.27 to 0.66). Women on iron supplements experienced a non statistical significant increase in side effects (RR 2.36; 95% CI 0.96 to 5.83), especially at doses greater than 60mg of elemental iron.

Clinical Guidelines:

The CDC and IOM recommend a multivitamin for pregnant women who did not consume an adequate diet. At minimum, the daily supplement should contain iron, calcium (at least 250 mg) and folate. The U.S. Preventive Services Task Force and Centers for Disease Prevention and Control recommend that all women of childbearing age take a daily vitamin supplement containing 400 to 800 mcg of folic acid from at least one month before conception through the first three months of pregnancy.[13,14] Patients who previously had a pregnancy affected by a neural tube defect should have 4 mg daily.

The World Health Organization (WHO) recommends daily oral iron and folic acid supplementation as part of the antenatal care to reduce the risk of low birth weight, maternal anemia and iron deficiency (strong recommendation).[7] In all settings, 30-60mg of elemental iron and 400 mcg of folic acid is recommended throughout pregnancy and started as early as possible. In addition, supplements to include other vitamin and minerals may be used to overcome other possible maternal micronutrient deficiencies.

- In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of pre-eclampsia in pregnant women, particularly amont those at higher risk of developing hypertension (Strong recommendation), in doses of 1.5-2.0 g elemental calcium/day from 20 weeks' gestation until the end of pregnancy.

The Institute for Clinical Symptoms Improvement (ICSI) states that there is no clinical evidence that universal supplementation with a multivitamin or prenatal vitamin in the preconception period or during pregnancy is beneficial.[13]

The following recommendations are provided from the Department of Veterans Affairs[15]:

Multivitamins:

- Multivitamin supplements should be taken one month preconceptually and should be continued through the first trimester (Strength of evidence C)
- Pregnant women taking supplements for a medical condition should continue that supplementation throughout pregnancy.
- Pregnant women on restrictive diets should have nutrition consultation to customize vitamin supplementation regimen.
- Folate supplements should be taken one month preconceptually, continued through the first trimester and should be administered as part of the multivitamin supplementation (Strength of recommendation A)

- Women who have delivered a child with an open neural tube defect should supplement their diets with 4 mg folate daily for at least one month prior to conception.
- Calcium supplementation may be considered to reduce the risk or preeclampsia in high risk women and those with baseline calcium intake (Strength of recommendation A).
- There is insufficient evidence to support the use of Omega 3 supplements in the prevention of preterm birth, preeclampsia, and low birth rate.
- Other dietary supplements should be used with caution and only after discussion with the provider.

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