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Dilute versus full-strength formula in exclusively formula-fed preterm or low birth weight infants

Authors: Basuki F, Hadiati DR, Turner T, McDonald S, Hakimi M

Review question

Is dilute formula milk (e.g. half the strength at double the volume) better tolerated than full-strength formula milk in the initial feeding of preterm babies for whom breast milk is not available?

Background

Babies born preterm (at less than 37 weeks' gestation) or with a low birth weight (less than 2500 grams) have special feeding requirements. Expressed breast milk is preferred, but preterm babies are often fed with formula milk because breast milk is not always available. The provision of artificial feeds varies considerably in preterm babies and there is concern that introducing full-strength formulas too early may lead to the retention of feed in the stomach, which is associated with feeding intolerance and necrotising enterocolitis, a severe bowel disorder.

Study characteristics

The evidence for this review is current as of 1 October 2018. We included three trials that compared dilute formula milk (half-strength, double-volume) with full-strength formula milk. The trials involved 102 preterm or low birth weight infants; two were conducted in the USA and one in India. The trials were small (14, 38 and 50 infants, respectively) and conducted between 25 and 30 years ago. The quality of two trials was judged to be

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poor due to insufficient information being provided in the trial publications, but judged to be moderate in the third trial (of 38 infants). None of the trials assessed necrotising enterocolitis as an outcome.

Key results

Infants receiving dilute formula (half-strength, double-volume) experienced fewer episodes of feeding intolerance and achieved full energy intake earlier than infants receiving full-strength formula (20 kcal/oz (~ 68 to 70 kcal/100 mL)).

Feeding intolerance

Two measures of feeding intolerance (abdominal distension and episodes of gastric residuals) were reported across the trials. Two trials (88 infants) provided data for abdominal distension and gastric residuals. Infants fed dilute formula experienced 19% (CI 16% to 23%) fewer episodes of abdominal distension (> 2 cm), equivalent to 0.67 episodes per infant in the half-strength group compared to 0.83 episodes in the full-strength group. It was not possible to combine data on gastric residuals but both trials reported fewer episodes of gastric residuals in the dilute formula group. The third trial (14 infants) only reported that there was no difference between the groups with respect to these two outcomes.

Time to establish full enteral feeding

In two trials (88 infants) infants receiving dilute formula experienced a 22% (CI 16% to 28%) reduction in the number of days required to reach an adequate energy intake (420 joules/kilogram), equivalent to 8 days in the half-strength group compared to 10.3 days in the full-strength group.

Certainty of evidence

In exclusively formula-fed preterm or low birth weight infants, low-certainty evidence shows that diluted formula may lead to an important reduction in the time taken to attain adequate enteral fluid and energy requirements, without increasing indicators of feeding intolerance. The clinical importance of the reduction in episodes of feeding intolerance is unclear. These findings are based on three small, old trials that may be of less relevance to current practice. A lack of data on other important outcomes, such as the incidence of necrotising enterocolitis and weight gain, limits the usefulness of the studies.

Diagnostic accuracy of total serum bile acids or individual bile acids for intrahepatic cholestasis of pregnancy in woman claiming pruritus

Authors: Manzotti C, Casazza G, Stimac T, Nikolova D, Gluud C

Review question

To assess and compare the diagnostic accuracy of total serum bile acids (TSBA) and some components of

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serum bile acid profile for the diagnosis of intrahepatic cholestasis of pregnancy in woman with onset of pruritus during pregnancy.

Background

'Diagnostic accuracy' means how well a test correctly identifies or rules out disease and informs subsequent decisions about treatment. Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disorder, in which bile (a digestive fluid) builds up in the liver, impairing the liver (intrahepatic) function. Intrahepatic cholestasis of pregnancy is possibly associated with an increased risk of premature delivery and fetal death, which seems to occur most often during the last weeks of pregnancy. This is why most clinicians choose to induce early delivery of the baby.

In clinical practice, presence of severe pruritus (itchiness) during late pregnancy and 'otherwise unexplained' abnormalities in serum liver tests, seems enough to support the diagnosis of intrahepatic cholestasis of pregnancy. However, excluding all other possible underlying diseases is not always easy; hence confirmation of the intrahepatic cholestasis of pregnancy diagnosis may be possible only after delivery, when spontaneous disappearance of pruritus and improvement of liver tests on blood exams usually occur.

Total serum bile acids (TSBA) are the most used biomarkers for intrahepatic cholestasis of pregnancy in clinical practice. Some components of the serum bile acid profile might provide more specific information than total serum bile acids when diagnosing the disease, defining its severity and monitoring its response to treatment.

Study characteristics

This review considered all evidence provided by studies that assess the diagnostic accuracy of total serum bile acids (TSBA) and any component of serum bile acid profile for intrahepatic cholestasis of pregnancy in woman claiming onset of pruritus during pregnancy.

We assessed all available reports from a wide, systematic search of databases of medical literature, irrespective of design, publication status, language, and study design. We finally included 16 studies, most of them assessing the accuracy (sensitivity and specificity) of TSBA with a cut-off of 10 µmol/L. Most studies had a case-control design, and these studies could have overestimated the diagnostic accuracy.

Key results

When considering the studies with a cut-off of 10 µmol/L for TSBA serum concentration, TSBA overall sensitivity (the ability to correctly identify women with the disease) ranged from 72% to 98% and specificity (the ability to correctly identify women without the disease) ranged from 81% to 97%. However, after performing two different analyses excluding studies with probably less reliable results, the diagnostic accuracy seemed lower.

We calculated the overall accuracy also of some components of serum bile acid profile, but the small number of studies and the high variability of the results led to very imprecise data.

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Quality of the evidence

Only one of the 16 included studies was performed and reported well (low risk of bias). The remaining 15 studies had problems with study design or reporting (high risk of bias). Only five studies seemed to show low concern regarding applicability of the results in clinical practice.

Conclusions

The overall high risk of bias, the existing concern regarding applicability of the results in clinical practice, and the poor uniformity of our results in the included studies prevents us from making recommendations and reaching definitive conclusions at present. Thus, we do not find any compelling evidence to recommend or refute the routine use of any of these tests in clinical practice. So far, the diagnostic accuracy of TSBA for intrahepatic cholestasis of pregnancy might have been overestimated. There were too few studies to permit a precise estimate of the accuracy of serum bile acid profile components. Further primary clinical research is mandatory. We need both further phase II and phase III diagnostic studies.

Is vitamin D supplementation beneficial or harmful for women during pregnancy?

Authors: Palacios C, Kostiuk LK, Peña-Rosas J

What is the issue?

It is not clear if vitamin D supplementation, alone or in combination with calcium or other vitamins and minerals, during pregnancy have benefits or harms to the mother or her offspring.

Why is this important?

Vitamin D is essential for human health, particularly bone, muscle contraction, nerve conduction, and general cellular function. Low concentrations of blood vitamin D in pregnant women have been associated with pregnancy complications. It is thought that additional vitamin D through supplementation during pregnancy might be needed to protect against pregnancy complications.

What was studied in the review?

This is an update of a review that was first published in 2012 and subsequently updated in 2016. This review evaluated the effect of supplementation with vitamin D alone or in combination with other micronutrients for women during pregnancy in comparison to placebo or no intervention, irrespective of dose, duration or time of commencement of supplementation or type of supplementation (oral or by injection).

What evidence did we find?

We searched for evidence (July 2018) and found 30 trials (involving 7033 women) for inclusion in this update.

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Evidence from 22 trials involving 3725 pregnant women suggest that supplementation with vitamin D alone during pregnancy probably reduces the risk of pre-eclampsia, gestational diabetes, and the risk of having a baby with low birthweight compared to placebo or no intervention and may make little or no difference in the risk of having a preterm birth. It may reduce the risk of maternal adverse events, such as severe postpartum haemorrhage, although it should be noted that this result was unexpected and based on a single trial.
Evidence from nine trials involving 1916 pregnant women suggest that supplementation with vitamin D and calcium probably reduces the risk for pre-eclampsia but may increase the risk of preterm birth. This slight potential harm warrants consideration in women receiving calcium supplementation as part of antenatal care.
Evidence from one study involving 1300 pregnant women suggest that supplementation with vitamin D plus other nutrients may make little or no difference in the risk of most outcomes evaluated.
Data on maternal adverse events were lacking in most trials.

What does this mean?

Supplementing pregnant women with vitamin D alone probably reduces the risk of pre-eclampsia, gestational diabetes, low birthweight and the risk of severe postpartum haemorrhage. It may make little or no difference in the risk of having a preterm birth < 37 weeks' gestation. Supplementing pregnant women with vitamin D and calcium probably reduces the risk of pre-eclampsia but may increase the risk of preterm births < 37 weeks (these findings warrant further research). Supplementing pregnant women with vitamin D and other nutrients may make little or no difference in the risk of preterm birth or low birthweight (less than 2500 g) and the effects for gestational diabetes and maternal adverse events are unclear. Additional rigorous high quality and larger randomised trials are required to evaluate the effects of vitamin D supplementation in pregnancy, particularly in relation to the risk of maternal adverse events.

Fetal fibronectin testing for reducing the risk of preterm birth

Authors: Berghella V, Saccone G

What is the issue?

To assess the effectiveness of management of pregnant women based on a knowledge of fetal fibronectin test results for preventing preterm birth, compared with not having that knowledge. Fetal fibronectin (FFN) acts as a ‘glue’ between the pregnancy and the uterus. Normally very low levels of FFN can be found in secretions of the vagina and cervix. Raised levels at or after 22 weeks have been associated with an increased risk of spontaneous preterm birth.

Why is this important?

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Preterm birth before 37 weeks is the main cause of sickness and death for newborn infants. Most women who give birth preterm have preterm labor symptoms such as contractions but many of the women with symptoms go on to deliver at term (37 weeks or more). Fetal fibronectin (FFN) is a test that can identify the women with symptoms of preterm labor who are most at risk for preterm birth. The level of FFN is measured in secretions from the vagina or cervix.

What evidence did we find?

We found six randomised controlled studies involving 546 women who were pregnant with one baby and were showing signs of preterm labor at between 23 to 34 weeks' gestation. We graded the following evidence as mainly low quality because of the low number of women in the studies and a wide variation in findings. We found that the number of births before 37 weeks may be slightly reduced when women and their doctors know the results of the FFN test (21.6% versus 29.2%; 4 trials; 357 women). However, knowledge of FFN results may make little or no difference for the other outcomes with available data, including: maternal hospitalization (5 trials; 441 women); use of uterine relaxants (tocolysis) to try to prevent labor; earlier preterm births; women's gestational age at delivery; babies with a birthweight less than 2500 g; newborn deaths; the number of babies with respiratory distress syndrome; giving steroids to mature the unborn babies' lungs; and number of days in a neonatal intensive care unit (NICU).

What does this mean?

This review of six studies did not find enough evidence to say whether or not the FFN test should be used in the management of women showing signs of preterm labor. A screening test such as FFN can only be considered effective if interventions based on the screening results, such as giving drugs to relax the uterus, reduce the number of preterm births. Further research should be encouraged.

If you have any questions or comments with regard to the above document please feel free to contact me.

Kind regards

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