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(54) Title: PRENATAL MILK-DERIVED COMPOSITION FOR PREVENTING THE RISK OF LOW BIRTHWEIGHT OF NEWBORNS

(57) Abstract: An object of the present invention is to develop a pharmaceutical composition or a food composition that ameliorates the low birthweight of newborns and prevents the birthweight from decreasing to a level below the average body weight (low body weight at birth) through improvement of nutrients during pregnancy. The present invention provides an agent for preventing low birthweight comprising milk phospholipids as an active ingredient, by which the low birthweight of newborns can be prevented.



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Description

Title of Invention: PRENATAL MILK-DERIVED COMPOSITION FOR PREVENTING THE RISK OF LOW BIRTHWEIGHT OF NEWBORNS

Technical Field

[0001] The present invention relates to the technical field of health foods and more specifically relates to the technical field of food compositions for preventing the risk of low birthweight of newborns.

Background Art

[0002] The problem of newborns with low birthweights of 2500 g or less at birth-, namely, low birthweight infants had been improving until 1975 in Japan. However, since 1980, the proportion of low birthweight infants among all newborns has been on the increase in Japan. The reasons behind this are as follows. Until then, adequate intake of sufficient nutrients during pregnancy has been recommended, but from 1975-1980, it begun to be indicated that excessive energy intake causes obesity or various metabolic problems, even among the general public in Japan. Pregnant women were warned that over-intake of nutrients during pregnancy could cause abnormal childbirth or pregnancy complications. Furthermore, a cosmetic requirement of pregnant women is also involved. Also, other reasons suggested are changes in the philosophy of obstetric medicine, increases in the number of neonates born at early pregnancy dates, increases in the incidence of smoking among women in their 20s or younger, effects from increases in multiple pregnancies, and the like (Non-patent literature 1).

[0003] Low body weights of newborns at birth are said to be related to diseases such as diabetes mellitus, hypertension, and coronary artery disease (Non Patent Literature 2) and are also said to be related to metabolic syndrome. Also, the respiratory functions of low birthweight infants are often immature, such that about 25% of such infants develop premature apnea. The resulting risk of the onset of a disorder in the brain or other organs has been suggested.

[0004] As described above, low body weight at birth imposes various burdens, disorders, or risks on newborns, so that prevention of low body weight at birth is thought to be important. As an effort to avoid such problems, it has been considered important to have good eating habits (eating breakfast and the like on a regular schedule) (Non Patent Literature 3). Also, a method for predicting and diagnosing low-bodyweight newborns at birth is reported in Patent literature 1, for example.

[0005] In addition, among nutritional necessities, such as for vitamins during pregnancy, the need for folic acid intake during pregnancy has already been particularly suggested for

over 40 years. The relationship between folic acid deficiency and inhibition of the formation of the central nervous system has been suggested. It is recommended to start folic acid intake before pregnancy, since this can lower the risk of neural tube defects (NTD) (Non Patent Literature 4). Furthermore, the relationship between vitamin B12 or folic acid deficiency in pregnant women and the low body weight of newborns at birth has also been suggested (Non Patent Literature 5).

Citation List

Patent Literature

[0006] PTL 1: JP Patent Publication (Kohyo) No. 2002-512047 A

Non Patent Literature

[0007] NPL 1: <http://www.aiiku.or.jp/aiiku/jigyo/contents/kaisetsu/ks0207/ks0207.htm>

NPL 2: Lancet 1999, Vol.353, No.9166, p.1789-1792

NPL 3: <http://www.asagumi.jp/asagohan/txt/1-6>

NPL 4: Report Concerning Reduction in the Risk of the Onset of Neural Tube Defects (December 2000) Conference concerning Risk of the Onset of Inborn Error

NPL 5: Asia Pac Journal of Clinical Nutrition 2006, Vol. 15, p. 538-543

Summary of Invention

Technical Problem

[0008] The first object of the present invention is to develop a pharmaceutical composition or a food composition for ameliorating the low birthweight of newborns so as to prevent the birthweight from decreasing to a level below the average birthweight of newborns (hereinafter, also referred to as the low birthweight of newborns) by improving nutrition during pregnancy.

[0009] Also, a second object of the present invention is to develop a pharmaceutical or food composition for preventing the low birthweight of newborns, which is intended for pregnant women at an increased risk of having low-birthweight newborns because of lack of nutritional balance (thought to be a background condition to the recent increases in the number of low body weight infants) due to the intake of snack food as a staple food and vitamin deficiencies.

[0010] Folic acid, which has been prescribed as a nutrient for pregnant women during pregnancy, is a water-soluble vitamin and known to be weak against light, acid, alkali, heat, and the like. Beverages (e.g., milk) containing folic acid and the like have been suggested to be problematic in that decreased folic acid concentrations are observed during lengthy storage, for example (Nihon Chikusan Gakkaiho 2009, Vol. 80, p. 41-45). Hence, it has been desired to provide a pharmaceutical product, a prenatal food for special dietary uses, or a prenatal nutritional supplementary food other than folic acid that provides safe and sure nutrition for pregnancy and is easier to preserve.

Solution to Problem

- [0011] Milk phospholipids (milk phospholipids or milk-derived phospholipids) are safe food ingredients, excellent in thermal stability and preservation quality. Successful prevention of the low birthweight of newborns through the intake of milk phospholipids contributes highly to the health of pregnant women and newborns.
- [0012] The present inventors have administered milk phospholipids to vitamin-B-deficient rats during pregnancy, and then evaluated the effects of vitamin Bs on the pregnant rats and the effects of vitamin Bs on rats in the fetal period based on body weights, body lengths, and organ weights of rats (babies) immediately after birth. As a result, the present inventors have discovered that rat babies are born with lower body weights in the case of vitamin-B-deficient pregnant rats (pregnant females), while lower body weights of rat babies can be prevented through administration of milk phospholipids to vitamin-B-deficient pregnant rats (pregnant females). Thus, the present inventors have completed the present invention.
- [0013] This specification includes part or all of the contents as disclosed in the specification and/or drawings of Japanese Patent Application No. 2009-143615, which is a priority document of the present application.

Advantageous Effects of Invention

- [0014] The present invention exerts an extremely good effect such that the low birthweight of newborns can be prevented with the use of a safe ingredient (milk phospholipids) ingested as a food. Furthermore, in general, fat-soluble vitamins are decomposed with more difficulty compared with water-soluble vitamins. Accordingly, it is thought that fat-soluble milk phospholipids are excellent in long-term preservation quality (do not decompose).

Brief Description of Drawings

- [0015] [fig.1]Fig. 1 shows the results of opening the abdominal cavity on day 20 of pregnancy, extracting fetuses, and then measuring the number and the body weight thereof.

Description of Embodiments

- [0016] The present invention encompasses an agent for preventing low birthweight comprising a milk phospholipid as an active ingredient, by which the low birthweight of newborns can be prevented. The present invention further encompasses an agent for reducing the risk of low birthweight comprising a milk phospholipid as an active ingredient, by which the risk of the low birthweight of newborns can be reduced. The present invention further encompasses an agent for preventing low birthweight comprising milk phospholipids as an active ingredient, by which the low birthweight of newborns due to the vitamin B deficiencies of pregnant women can be prevented.

Also, the present invention encompasses an agent for reducing the risk of low birthweight comprising a milk phospholipid as an active ingredient, by which the risk of the low birthweight of newborns due to vitamin B deficiencies of pregnant woman can be reduced.

[0017] Also, the present invention encompasses a prenatal medicine for reducing the risk for a newborn to have diabetes mellitus, hypertension, or coronary artery disease associated with the low birthweight of newborns after the growth of the newborns through administration thereof to their mother.

1. Prevention of low birthweight of newborns

Intake of a vitamin-B-deficient diet (deficiencies in vitamin Bs) during pregnancy is highly likely to result in the low birthweight of newborns of the relevant pregnant woman. Surprisingly, the present inventors have discovered that through administration of milk phospholipids to such a pregnant woman who has a vitamin-B-deficient diet, low birthweight of a newborn can be significantly suppressed or prevented.

[0018] The composition of the present invention for preventing the low birthweight of newborns comprises milk phospholipids as an active ingredient and encompasses:

(1) an agent for preventing low birthweight, by which the low birthweight of newborns can be prevented;

(2) an agent for reducing the risk of the low birthweight, by which the risk of low birthweight of newborns can be reduced;

(3) an agent for preventing low birthweight, by which the low birthweight of newborns due to vitamin B deficiencies of a pregnant woman can be prevented; and

(4) an agent for reducing the risk of low birthweight, by which the risk of the low birthweight of newborns due to vitamin B deficiencies of a pregnant woman can be reduced.

1-1. Composition for preventing the low birthweight of newborns

In the present invention, an example of an active ingredient of the composition for preventing low birthweight of newborns is a milk phospholipid. An example of a milk phospholipid is obtained by extraction of a lipid ingredient from milk using ethanol or the like, followed by extraction of the milk phospholipid using acetone.

[0019] For example, a milk-derived phospholipid can be prepared by a known method as disclosed in JP Patent Publication (Kokai) No. 2002-226394 A. Specifically, the milk-derived phospholipid can be prepared by solvent extraction according to a known method { "Lipid Chemistry (Shishitsu no Kagaku) (Seikagaku Jikken Koza (Biochemical Experimental Lecture Series) 3)," Ed., The Japanese Biochemical Society, p. 23, TOKYO KAGAKU DOZIN CO., LTD, 1974; "lipid II phospholipid (New Seikagaku Jikken Koza (New Biochemical Experimental Lecture Series) 4),"

Ed., The Japanese Biochemical Society, p. 7, TOKYO KAGAKU DOZIN CO., LTD, 1991} from butter milk, which is a byproduct of butter production; whey, which is a byproduct of cheese production; or defatted milk. Alternatively, the milk-derived phospholipid can be prepared by fractionation of the extract (obtained by the aforementioned solvent extraction) using various types of chromatography. For example, the milk-derived phospholipid can also be obtained as an insoluble fraction of acetone (solvent) from cream or butter, or butter serum, which is a byproduct of butter oil production. Butter serum is also used in the field of market milk and thus is available (e.g., New Zealand, Tatua). Butter serum has a high content of MFGM, in which phospholipids are localized, and thus is suitable as a raw material for extraction of phospholipids.

[0020] For separation of phospholipids from butter serum, the property of phospholipids being insoluble in acetone is used. Through a plurality of acetone extractions, an acetone-soluble fraction containing neutral lipids is removed and then an acetone-insoluble fraction containing concentrated phospholipids is obtained. The acetone-insoluble fraction is subjected to vacuum concentration to remove acetone and then the concentrate is subjected to freeze drying after sterilization. The dried product is pulverized, so that a milk-derived phospholipid fraction is obtained. For example, the composition of the thus obtained phospholipid fraction contains 85% (% by weight) phospholipids. In the phospholipid fraction, an ingredient containing choline such as phosphatidyl choline and sphingomyelin is present.

[0021] Furthermore, for milk phospholipids, "milk phospholipid concentrate" (containing about 5% by weight choline; 85% by weight lipids, 10% by weight ash content, 4% by weight carbohydrate, and 1% by weight moisture) or "Hohoemi (smile) (Meiji Dairies Corporation)" that is a dairy product containing milk phospholipids can also be used.

2. Prenatal medicine

The medicine of the present invention is:

(1) a prenatal medicine for preventing the low birthweight of newborns (agent for preventing low birthweight) or (2) a prenatal medicine for reducing the risk of the low birthweight of newborns (agent for reducing the risk of low birthweight); or

(3) a prenatal medicine for reducing the risk for a newborn to have a disease associated with the low birthweight of newborns after growth through administration of the prenatal medicine to a pregnant woman who is the mother of the newborn.

[0022] Examples of the medicine of the present invention comprising milk phospholipids as an active ingredient include (1) a prenatal medicine (agent for preventing low birthweight) for preventing the low birthweight of newborns, (2) a prenatal medicine (agent for reducing the risk of low birthweight) for reducing the risk of the low birthweight of newborns, and (3) a prenatal medicine for reducing the risk for a

newborn to have a disease associated with the low birthweight of newborns after growth through administration of the prenatal medicine to a pregnant woman who is the mother of the newborn.

[0023] The medicine of the present invention can be formulated into appropriate dosage forms such as powders, granules, tablets, capsules, and solutions. Upon formulation, auxiliary agents that are generally used for formulation may be added, such as an excipient, a binder, a disintegrator, and a lubricant. Examples of an excipient include starch, lactose, saccharose, methylcellulose, carboxymethylcellulose, sodium alginate, calcium hydrogen phosphate, synthetic aluminum silicate, microcrystalline cellulose, polyvinylpyrrolidone (PVP), and hydroxypropyl starch (HPS). Also, examples of a binder include starch, microcrystalline cellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (PVP), powdered acacia, gelatin, dextrose, and an aqueous solution of saccharose or the like, or aqueous solutions or ethanol solutions thereof. Examples of a disintegrator include starch, carboxymethylcellulose, carboxymethylcellulose calcium, microcrystalline cellulose, hydroxypropyl starch, and calcium phosphate. Furthermore, examples of a lubricant include carnauba wax, light anhydrous silicic acid, synthetic aluminum silicate, natural aluminum silicate, synthetic magnesium silicate, hardened oil, a derivative of hydrogenated vegetable oil (Sterotex HM), sesame oil, white beeswax, titanium oxide, dry aluminium hydroxide-gel stearic acid, calcium stearate, magnesium stearate, talc, calcium hydrogen phosphate, and sodium lauryl sulfate.

2-1. Dosage form of the medicine of the present invention

The medicine of the present invention, which is specifically (1) a prenatal medicine for preventing the low birthweight of newborns, (2) a prenatal medicine for reducing the risk of the low birthweight of newborns, or (3) a prenatal medicine for reducing the risk for a newborn to have a disease associated with the low birthweight of newborns after growth through administration of the prenatal medicine to a pregnant woman who is the mother of the newborn, can be administered orally or parenterally and can be preferably administered orally.

[0024] Also, regarding the oral dosage of the medicine of the present invention, for example, the dosage of choline desirably ranges from 60 mg/day to 3.5 g/day, preferably ranges from 100 mg/day to 3.5 g/day, more preferably ranges from 200 mg/day to 3.5 g/day, and further preferably ranges from 350 mg/day to 3.5 g/day. The dosage of a "milk phospholipid concentrate" (containing about 5% by weight choline; 85% by weight lipids, 10% by weight ash content, 4% by weight carbohydrate, and 1% by weight moisture) desirably ranges from 1.4 g/day to 75 g/day, preferably ranges from 2.4 g/day to 75 g/day, more preferably ranges from 4.8 g/day to 75 g/day, and further preferably ranges from 7.5 g/day to 75 g/day (e.g., American Journal of Clinical

Nutrition 2005, 82, p. 111-117; American Journal of Clinical Nutrition 2006, Vol. 83, p. 905-911; European Journal of Nutrition, 2007, Vol. 46, p. 300-306, Dietary Reference Intakes, p. 411).

[0025] In the present invention, the intake of a prenatal medicine for preventing the low birthweight of newborns is desirably initiated before pregnancy. It is desired to intake the prenatal medicine at least once throughout pregnancy, and preferably to intake the same continuously throughout pregnancy (e.g., everyday).

2-2. Subjects for administration of the medicine of the present invention

The medicine of the present invention, which is specifically (1) a prenatal medicine (agent for preventing low birthweight) for preventing the low birthweight of newborns, (2) a prenatal medicine (agent for reducing the risk of low birthweight) for reducing the risk of low birthweight of newborns, or (3) a prenatal medicine for reducing the risk for a newborn to have a disease associated with the low birthweight of newborns after growth through administration of the prenatal medicine to a pregnant woman who is the mother of the newborn, can be administered to all pregnant women. The medicine of the present invention can be administered particularly to pregnant women who have an unbalanced intake of nutrients. Specific examples of such pregnant women include pregnant women with vitamin deficiencies and further specific examples thereof include pregnant women who are vegetarians and pregnant women with vitamin B deficiencies. Here, the term "vitamin B deficiencies" refers to folic acid deficiency, vitamin B2 deficiency, vitamin B6 deficiency, and vitamin B12 deficiency.

3. Prenatal food for special dietary uses or prenatal nutritional supplementary food

The food for special dietary uses or the nutritional supplementary food of the present invention is (1) a prenatal food for special dietary uses or a prenatal nutritional supplementary food for preventing the low birthweight of newborns, (2) a prenatal food for special dietary uses or a prenatal nutritional supplementary food for reducing the risk of the low birthweight of newborns, or (3) a prenatal food for special dietary uses or a prenatal nutritional supplementary food for reducing the risk for a newborn to have a disease associated with the low birthweight of newborns after the growth through administration of the prenatal food or the prenatal nutritional supplementary food to a pregnant woman who is the mother of the newborn.

[0026] The food for special dietary uses or the nutritional supplementary food of the present invention comprises a milk phospholipid as an active ingredient and may be in any form of solid (e.g., powders and granules), paste, liquid, or suspension. For example, when the food is formulated into a drinkable preparation, an additive such as a sweetener, an acidulant, a vitamin preparation, and others that are generally used for production of drinkable preparations may also be added.

[0027] The food for special dietary uses or the nutritional supplementary food of the present

invention can be formulated into a supplement in an appropriate dosage form such as powders, granules, tablets, capsules, or solutions.

[0028] Moreover, the food for special dietary uses or the nutritional supplementary food of the present invention may be in the form of a food additive comprising a phospholipid as an active ingredient for preparation of a prenatal food for special dietary uses or a prenatal nutritional supplementary food.

[0029] Regarding the intake of the food for special dietary uses or the nutritional supplementary food of the present invention, the intake of choline desirably ranges from 60 mg/day to 3.5 g/day, preferably ranges from 100 mg/day to 3.5 g/day, more preferably ranges from 200 mg/day to 3.5 g/day, and further preferably ranges from 350 mg/day to 3.5 g/day, and the intake of a "milk phospholipid concentrate" (containing about 5% by weight choline, 85% by weight lipids, 10% by weight ash content, 4% by weight carbohydrates, and 1% by weight moisture) desirably ranges from 1.4 g/day to 75 g/day, preferably ranges from 2.4 g/day to 75 g/day, more preferably ranges from 4.8 g/day to 75 g/day, and further preferably ranges from 7.5 g/day to 75 g/day (e.g., American Journal of Clinical Nutrition 2005, 82, p. 111-117; American Journal of Clinical Nutrition 2006, Vol. 83, p. 905-911; European Journal of Nutrition, 2007, Vol. 46, p. 300-306, Dietary Reference Intakes, p. 411).

Examples

[0030] {Example 1} Effect of milk phospholipid intake during pregnancy

Experimental method

This experiment was conducted by dividing rats into 4 groups and using 8 rats for each instance of breeding in total of 4 instances of breeding. The rat body weight ranged from 155 g to 165 g at the beginning of the experiment and ranged from 240 g to 290 g at the completion of the experiment (duration of pregnancy). At this time, no significant differences were present in the body weights of each group.

(1) 9-week-old female Wistar rats were fed ad libitum with a low vitamin diet (low vitamin diet: feed prepared by removing vitamin B2, folic acid, vitamin B12, and choline bitartrate from AIN93G vitamin mix) or a control diet (control group: AIN93G) for 1 week. (Table 1)

(2) 10-week-old female Wistar rats were crossed.

(3) The day on which crossing (plug) had been confirmed was designated day 0 of gestation. Each group was fed ad libitum with test diets (AIN93G, low vitamin diet, low vitamin diet + milk phospholipids (2.6% by weight; choline content was about 40 mg/g), the low vitamin diet + choline bitartrate (0.25% by weight)). They were fed ad libitum with the test diets until day 20 of gestation. In addition, the choline concentration was 0.1% by weight in the low vitamin diet + milk phospholipids, the low

vitamin diet + choline bitartrate, and AIN93G.

(4) On day 20 of gestation, about 0.3 ml of blood was collected via a vein, laparotomy was performed, fetuses were extracted, and then their body weight was measured. In addition, the general number of litters was determined to be 12 +/- 3 (rats beyond such number were excluded) and then the groups were compared with each other. For statistical analysis, a multiple comparison (Post-hoc: Scheffe) test was conducted using one-way analysis of variance of Statview (SAS).

[0031] [Table 1]

Composition of feed [%]	AIN93G (control)	Low vitamin diet	Low vitamin diet + choline bitartrate	Low vitamin diet + milk phospholipids
Corn starch	37.9486	38.1986	37.9486	38.1986
Casein	20	20	20	20
Gelatinized corn starch	15	15	15	15
Sucrose	10	10	10	10
Purified soybean oil	7	7	7	4.4
Cellulose	5	5	5	5
Mineral mix	3.5	3.5	3.5	3.5
Vitamin mix	1	0	0	0
*Vitamin mix for low vitamin diet	0	1	1	1
L-cystine	0.3	0.3	0.3	0.3
Phospholipid (ML)	0	0	0	2.6
Choline bitartrate	0.25	0	0.25	0
t-butylhydroquinone	0.0014	0.0014	0.0014	0.0014

*The term "vitamin mix for low vitamin diet" refers to a vitamin mix prepared by removing vitamin B2, vitamin B12, and folic acid from the AIN93G vitamin mix.

Experimental result

Because of the intake of the low vitamin diet, fetal body weights were lowered (Fig. 1). However, because of the intake of the low-vitamin diet supplemented with milk phospholipids, fetal body weights were improved such that they were on the increase (Fig. 1 and Table 2).

[0032]

[Table 2]

	Fetal body weight [g]	Standard deviation [g]
Control group (n=68)	3.156	0.288
Low vitamin diet group (n = 67)	3.000	0.258
Low vitamin diet + choline bitartrate group (n = 70)	3.068	0.217
Low vitamin diet + milk phospholipid group (n = 34)	3.199	0.249

It was demonstrated by this experiment that the intake of vitamins is required for fetal development. It was further demonstrated that the intake of milk phospholipids can improve the underdevelopment of fetuses due to vitamin deficiencies.

Industrial Applicability

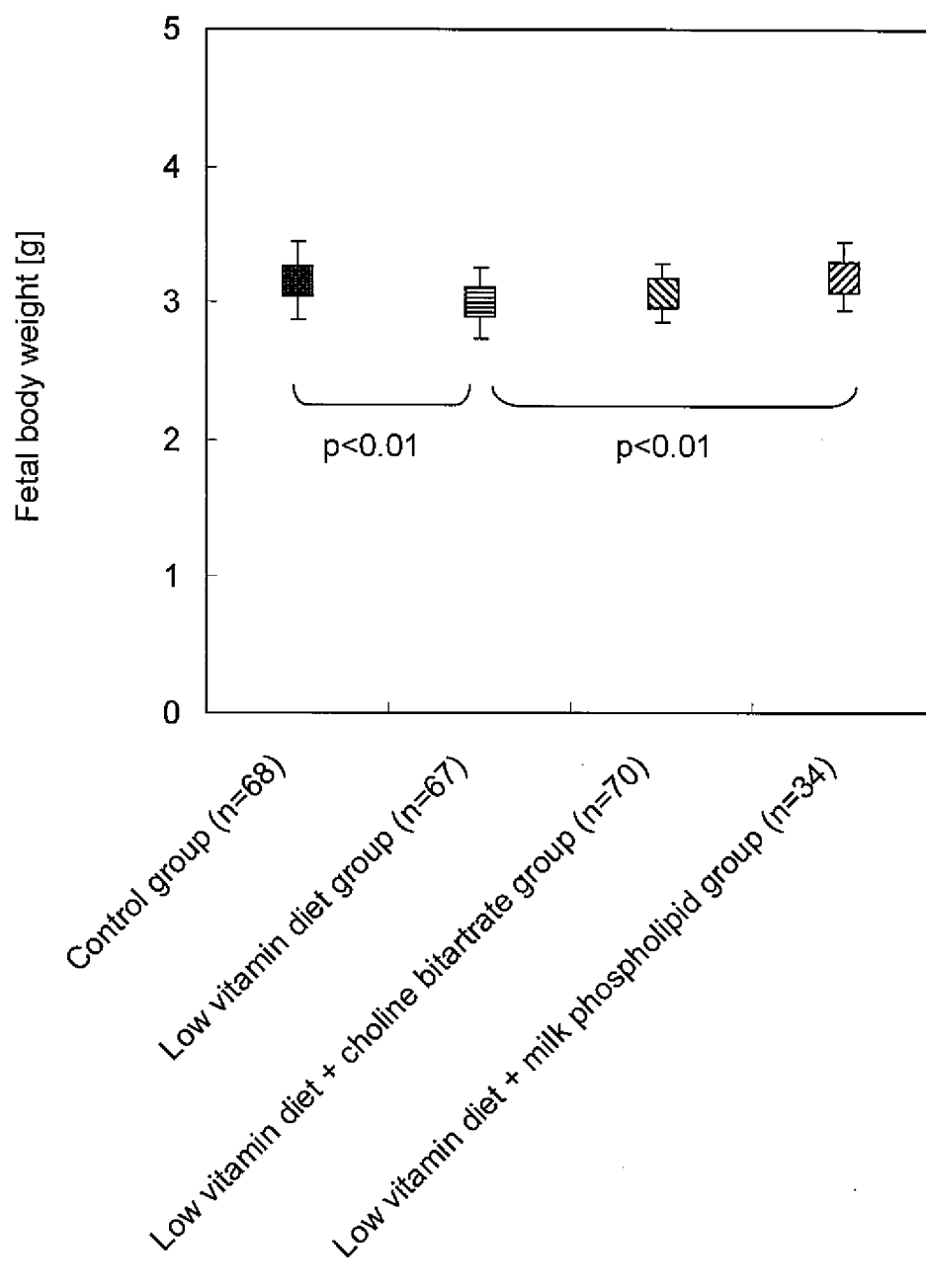
[0033] The prenatal medicine, the food for special dietary uses, or the nutritional supplementary food of the present invention exerts excellent effects such that low birthweight of newborns can be prevented. Hence, the prenatal medicine, the food for special dietary uses, or the nutritional supplementary food can be used in the pharmaceutical or food production industries.

[0034] All publications, patents, and patent applications cited herein are incorporated herein by reference in their entirety.

Claims

- [Claim 1] A prenatal medicine comprising a milk-derived phospholipid as an active ingredient, by which the low birthweight of a newborn from a pregnant woman is prevented.
- [Claim 2] A prenatal medicine comprising a milk-derived phospholipid as an active ingredient, by which the risk of low birthweight of a newborn from a pregnant woman is prevented.
- [Claim 3] The medicine according to claim 1 or 2, which is a medicine for a pregnant woman whose intake of vitamin B and folic acid is insufficient.
- [Claim 4] The medicine according to any one of claims 1 to 3, wherein the milk-derived phospholipids include sphingomyelin and/or phosphatidylcholine.
- [Claim 5] The medicine according to any one of claims 1 to 4, wherein the choline content is at least 60 mg/day.
- [Claim 6] A prenatal food for special dietary uses or a prenatal nutritional supplementary food comprising milk-derived phospholipids as an active ingredient, by which the risk of the low birthweight of a newborn from a pregnant woman is prevented.
- [Claim 7] The prenatal food for special dietary uses or the prenatal nutritional supplementary food according to claim 6, which is used for a pregnant woman whose intake of vitamin B and folic acid is insufficient.
- [Claim 8] The prenatal food for special dietary uses or the prenatal nutritional supplementary food according to claim 6 or 7, wherein the milk-derived phospholipids include sphingomyelin and/or phosphatidylcholine.
- [Claim 9] The prenatal food for special dietary uses or the prenatal nutritional supplementary food according to any one of claims 6 to 8, wherein the choline content is at least 60 mg/day.
- [Claim 10] A food additive for preparation of a prenatal food for special dietary uses or a prenatal nutritional supplementary food preventing the risk of the low birthweight of a newborn, comprising a milk-derived phospholipid as an active ingredient.

[Fig. 1]



INTERNATIONAL SEARCH REPORT

International application No
PCT/JP2010/003959

A. CLASSIFICATION OF SUBJECT MATTER

INV. A23L1/29 A23L1/30 A61K31/688 A61K31/685 A61P43/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data, BIOSIS, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	THOMAS J D ET AL: "Prenatal choline supplementation mitigates the adverse effects of prenatal alcohol exposure on development in rats" NEUROTOXICOLOGY AND TERATOLOGY, PERGAMON, ELMSFORD, NY, US LNKD- DOI:10.1016/J.NTT.2009.07.002, vol. 31, no. 5, 1 September 2009 (2009-09-01), pages 303-311, XP026715127 ISSN: 0892-0362 [retrieved on 2009-07-16] page 303, left-hand column, paragraph 1 - right-hand column, paragraph 1 page 308, right-hand column, paragraph 2 ----- -/--	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/JP2010/003959

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