The CLIMB (Complex Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel randomised controlled trial to investigate the effect of supplementation of complex lipids in pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring

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To cite: Huang S, Mo T-T, Norris T, et al. The CLIMB (Complex Lipids In Mothers and Babies) study: protocol for a multicentre, three-group, parallel randomised controlled trial to investigate the effect of supplementation of complex lipids in pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring. BMJ Open 2017;7:e016637. doi:10.1136/bmjopen-2017-016637

ABSTRACT

Introduction Complex lipids are important constituents of the central nervous system. Studies have shown that supplementation with complex milk lipids (CML) in pregnancy may increase the level of fetal gangliosides (GA), with the potential to improve cognitive outcomes.

Methods and analysis We aim to recruit approximately 1500 pregnant women in the first trimester (11–14 weeks) and randomise them into one of the three treatment groups: standard maternal milk formulation, CML-enhanced maternal milk formulation or no maternal milk intervention with standard pregnancy advice (ie, the standard care). Maternal lifestyle and demographic data will be collected throughout the pregnancy, as well as biological samples (eg, blood, hair, urine, buccal smear, cord blood, cord and placenta samples). Data from standard obstetric care recorded in hospital maternity notes (eg, ultrasound reports, results of oral glucose tolerance test and pregnancy outcome data) will also be extracted. Postnatal follow-up will be at 6 weeks and 12 months of age, at which point infant cognitive development will be assessed (Bayley Scales of Infant Development I).

Ethics and dissemination This project was approved by the Ethics Committee of Chongqing Medical University. Dissemination of findings will take the form of publications in peer-reviewed journals and presentations at national and international conferences.

Trial registration number ChiCTR-IOR-16007700; Pre-results.

Strengths and limitations of this study

► To our knowledge, the CLIMB (Complex Lipids In Mothers and Babies) study is the first large clinical trial to perform interventions with complex milk lipids (CML) during pregnancy in humans.

► In the offspring, data will be collected both in prenatal and postnatal life (eg, anthropometry, nutrition, cognitive outcomes) and we will also collect data relating to maternal lifestyle, health, living environment and nutrition predelivery and postdelivery. Measures and samples will be collected in different periods of pregnancy, therefore allowing us to trace dynamic changes in outcomes in response to specific exposures at different time points.

► A wide range of women will be recruited to gain as representative sample as possible; however, a potential limitation is that the study area is limited to a single city in China (Chongqing).

INTRODUCTION

Gangliosides (GA) are a set of sialic acid containing glycosphingolipids found in almost all vertebrate tissue membranes, but most abundantly in the nervous system.1 2 Previous reviews confirm an essential role of GA in brain structure and function.3–5 They are also reported to provide protection from inflammation, neurodegeneration,6 7 apoptosis and tumours,8 9 to accelerate neural development of the newborn10–13 and to contribute to learning and memory.14–16 In addition, decreased levels of GA contribute to
the development of Alzheimer’s disease and Huntington’s disease. Complex lipids, including GA, are important components of neuronal tissues. Complex milk lipids (CML), as a source of GA, have potential benefits for brain development. The rate of GA accretion in the developing brain is highest in utero and in early neonatal life. Preclinical research has shown that CML are transferred across the placenta and as such, an increased maternal intake of CML in pregnancy has been associated with increases in fetal GA levels. Human milk fat globules are stabilised by the milk fat globule membrane (MFGM), which contains complex milk lipids such as glycerophospholipids, sphingomyelin, GA and cerebrosides. Infant dietary GA intakes are highest in breastfed infants, and research in animal models and small-scale infant nutrition intervention studies have shown that supplementation of CML (containing GA) in the neonatal period may improve cognitive outcomes.

Therefore, we hypothesise that a higher maternal intake of CML in pregnancy, serving as an additional source of GA, will increase GA status in both mother and offspring, with potential benefits relating to brain development and general health in the infant, especially during the first year of life. Accordingly, we have initiated a randomised controlled trial of CML-enhanced maternal milk supplementation in pregnancy, the CLIMB (Complex Lipids In Mothers and Babies) study, in order to investigate whether increased prenatal maternal intake of CML impacts on maternal or infant complex lipid status and subsequent infant cognitive development.

Objectives
The CLIMB study is a multicentre, three-group, parallel randomised controlled trial. We aim to recruit 1500 pregnant women and randomise them into three treatment groups. Our primary objectives are: (1) to evaluate the impact of maternal dietary CML intake on maternal and infant complex lipid status by comparing outcomes of product A with product B and a reference group and (2) to investigate the benefits of the fortified maternal milk products (containing CML) on maternal health and nutritional status, and general infant health and neurodevelopment.

METHODS AND DESIGN

Study design
Recruitment of the 1500 women begins in September 2015 with the aim of completing all assessments by May 2018. The women will be randomized into one of the three treatment groups:

- Control group: standard maternal milk formulation (product A; table 1) which provides a minimum of 2 mg GA per serving and 4 mg GA per day.
- Intervention group: CML-enhanced maternal milk (product B; table 1) formulated to provide a minimum of 4 mg GA per serving and 8 mg GA per day. CML-enhanced maternal milk (Anmum maternal milk, Fonterra Co-operative Limited, New Zealand) contains Beta Serum (Nuelipid supplied by Fonterra Co-operative Limited), a byproduct from the manufacturing of anhydrous milk fat and a source of MFGM complex lipids.
- Reference group: no maternal milk with standard obstetric care including prenatal folic acid supplementations.

All mothers and infants will be followed up until 12 months postdelivery.

Study enrolment will take place at the First Affiliated Hospital of Chongqing Medical University (FCQMU) and Chongqing Health Centre for Women and Children (CHC). After delivery, infant follow-up will take place at the CHC. In total, there are five clinic visits (see tables 2 and 3)—three will take place during pregnancy and...
Table 2  Maternal measures and samples during pregnancy

<table>
<thead>
<tr>
<th>Data collected</th>
<th>Clinic visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>11–14 weeks</td>
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<tr>
<td>Abdominal ultrasound</td>
<td>√</td>
</tr>
<tr>
<td>Lifestyle Information</td>
<td>√</td>
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<tr>
<td>Nutritional assessment—food frequency questionnaire</td>
<td>√</td>
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<tr>
<td>Nutritional assessment—24 hours food recall</td>
<td>√</td>
</tr>
<tr>
<td>Maternal anthropometry</td>
<td>√</td>
</tr>
<tr>
<td>Bloods</td>
<td>√</td>
</tr>
<tr>
<td>Urine*</td>
<td>√</td>
</tr>
<tr>
<td>Hair sample*</td>
<td>√</td>
</tr>
<tr>
<td>Buccal smear†</td>
<td>√</td>
</tr>
<tr>
<td>Oral glucose tolerance test</td>
<td></td>
</tr>
<tr>
<td>Paternal buccal smear† (optional)</td>
<td>√</td>
</tr>
</tbody>
</table>

*For identification of metabolomic biomarkers.
†For identification of epigenetic biomarkers and assessment of the effect of pregnancy maternal epigenomic profile.

Table 3  Maternal and infant measures and samples after delivery

<table>
<thead>
<tr>
<th>Data collected</th>
<th>Clinic visit</th>
</tr>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Birth</td>
</tr>
<tr>
<td>Maternal (postdelivery)</td>
<td></td>
</tr>
<tr>
<td>Nutritional assessment—food frequency questionnaire</td>
<td></td>
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<tr>
<td>Nutritional assessment—24 hours food recall</td>
<td></td>
</tr>
<tr>
<td>Buccal smear*</td>
<td>√</td>
</tr>
<tr>
<td>Maternal anthropometry</td>
<td>√</td>
</tr>
<tr>
<td>Maternal blood</td>
<td>√</td>
</tr>
<tr>
<td>Mode of delivery, gestational age, pregnancy outcome</td>
<td></td>
</tr>
<tr>
<td>Infancy</td>
<td></td>
</tr>
<tr>
<td>Infant feeding and health</td>
<td>√</td>
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<tr>
<td>Cord blood, cord and placenta sample collection</td>
<td>√</td>
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<tr>
<td>Anthropometry</td>
<td>√</td>
</tr>
<tr>
<td>Buccal smear*</td>
<td>√</td>
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<tr>
<td>Bayley scales of infant development I</td>
<td></td>
</tr>
</tbody>
</table>

*For identification of epigenetic biomarkers and assessment of the effect of pregnancy maternal epigenomic profile.
current study, but which may also be used in the future for commercial purposes or for research unrelated to this study. Women will be randomised into one of the groups with a unique trial identity code number and allocated to a specific research nurse for the duration of the study, in an attempt to minimise the loss to follow-up rate.

**Inclusion and exclusion criteria**

Women who are 11–14 weeks pregnant will be recruited from maternity clinics. Further inclusion criteria include: gravidas aged 20–40 years, singleton pregnancy, living in Chongqing municipality and able to provide written informed consent. Exclusion criteria are: previous pregnancy with complications which resulted in delivery before 32 weeks, allergy to milk and severe milk aversion or lactose intolerance.

**Withdrawal**

All participants are free to withdraw from the study at any time, for any reason, and without any impact on future medical care. If a participant is withdrawn before completing the study, the date of withdrawal and the reason will be entered into the case report form (CRF). All previous collected data (including measures and samples) will remain in storage for later analysis. If a participant does not return for a scheduled visit, every effort (eg, phone call, WeChat and QQ) will be made to contact them. If the participant refuses to attend, she will be considered as having dropped out. If the participant withdraws from the study and withdras consent, no intervention will be performed and no additional data will be collected.

**Randomisation and allocation concealment**

At clinic visit 1, all eligible participants will be randomised via the MedSciNet AB (Stockholm, Sweden) Interactive Web Response System, to either the control, intervention or reference group. The system will assign each participant to a unique trial number, consistent with either one of the treatment groups or the reference group. Randomisation will ensure equal allocation of participants to each of the groups.

The randomisation sequence for the treatment groups will be concealed until interventions are all assigned and recruitment, data collection and data cleaning are complete. The central list that details the numbered cans of product A or product B will be produced by Fonterra Co-operative Group Ltd, New Zealand.

**Intervention and comparison**

The intervention period begins at the time of recruitment (11–14 weeks of gestation) and ends when the baby is born, allowing the impact of maternal and fetal nutrition during gestation, a sensitive window for brain development, to be investigated.

Pregnant women will be assigned to either a reference group, or to one of the two intervention groups, milk powder of product A or product B. The only difference between products A and B, both reduced-fat formulations, is the amount of CML contained in each, with product B having a restored level of CML to that of full-fat milk (table 1). Both treatment groups are instructed to consume 37.5 g of the milk powder twice a day, with clear instructions written on the can of milk powder. These instructions are verbally communicated by the research nurse. The reference group (as well as both treatment groups) will receive standard pregnancy care (including regular monitoring and supplementation with 400 µg of folic acid, based on general dietary recommendation for pregnancy). To improve study adherence, participants in the intervention groups will be asked to return, at each clinic visit, the product cans along with the forms provided to document daily consumption of the product. Furthermore, we will utilise popular Chinese social media platforms to provide weekly pregnancy health and nutrition suggestions, specific to pregnancy, and also to facilitate one-to-one communication between nurses and participants. Finally, reminder messages will be sent 3 days prior to each visit. Follow-up will continue until the child is 12 months of age. This age was chosen as it enables the effect of an improved maternal nutrition during pregnancy on infant cognitive development, to be assessed. Cognitive development will be assessed via the Bayley Scales of Infant Development I (BSID-I). A further consideration in selecting the follow-up period was that after this point in infancy, it is thought that other influences affecting infant development (eg, variability of their own diet and environment) may potentially exert large effects on the outcome.

**Blinding**

Participants will be allocated to either product A (control), product B (intervention) or to the reference group. If the participant is randomised to one of the treatment groups, they will be blinded to which of the two groups they have been allocated to. Investigators and the specific research nurse allocated to each enrolled woman will be aware of which participants have been randomised to standard care (vs products A and B). However, they will remain blinded to the product A/B allocation from the time of randomisation until either the subject is unblinded or the database is unlocked. As for any other assessments (excluding the food frequency questionnaire and 24-hour food recall), staff will be completely blinded.

**DATA COLLECTION AND ANALYSIS**

**Measures and samples**

The primary maternal outcome is serum complex lipid levels (eg, GA determined by ultra performance liquid chromatography–tandem mass spectrometer) in maternal blood. The secondary maternal outcomes are maternal nutritional status (eg, blood routine, micronutrient status in blood), clinical indicators of maternal health (eg, blood pressure, glucose tolerance), gestational weight gain and outcomes of pregnancy, including complications (eg, gestational diabetes mellitus, gestational hypertension).
The primary offspring outcomes are infant cognitive development (assessed by BSID-I) and general infant health (infant growth, eg, height, weight and skinfold thickness). Secondary offspring outcomes include fetal size, growth and outcomes at birth. Additional samples include those for subsequent epigenetic analysis (eg, buccal smears of both mother and infant is taken for bisulfite sequencing), will be taken (tables 2 and 3).

**Quality control**

Source documents shall be filed at the site and may include, but are not limited to consent forms, current medical records, laboratory results and pharmacy records. The CRF will serve as source for some of these data. Only trial staff listed on the Site Responsibility Delegation Log will have access to trial documentation other than the regulatory requirements listed below. The CRF and all source documents, including progress notes and copies of laboratory and medical test results, will be made available at any time for review by the sponsor’s designed and inspection by relevant regulatory authorities.

All paper forms shall be filled in using gel pen. Errors shall be crossed out but not obliterated and the correction inserted, initialled and dated. The recruiting clinician shall sign a declaration ensuring accuracy of data recorded in the CRF. CRFs will be held securely in a locked cabinet in a locked room. Real-time electronic data will be created as soon as local data is imported into the database. Blood and/or serum samples will be collected and prepared by employees of the institution and stored in a regulated −80°C freezer.

**Data management**

At the time of randomization, each participant will be assigned a unique trial identity code number. The number will be for use on the CRF, other trial documents and the password-protected electronic database (MedSciNet). The documents and database will also incorporate their initials and date of birth. The investigators will also keep a screening log with details of all patients screened for the trial (including those who were and were not subsequently randomised) with their name, date of birth, local hospital number and trial number.

The investigators and institutions will permit monitoring, audits, institutional ethics committee/institutional review board review, and regulatory inspections, providing direct access to source data/documents. CRFs will otherwise be restricted to those personnel approved by the Principal Investigator and recorded on the ‘Site Responsibility Delegation Log’.

**Statistical methods**

On the basis of previously reported serum GA measures,


| 30 | 33 |

a sample size of 500 participants in each group is sufficient to detect a difference of 25% SDs, with a study power of 80%, and at a significance level of 5%. The loss to follow-up rate is expected to be 20%. This sample size enables adjustment for three pair-wise comparisons.

Treatment evaluation will be performed on the principle of intention to treat. Statistical analyses will be conducted using SAS V.9.3 software (SAS Institute, Cary, North Carolina, USA). All statistical tests will be two-sided, with significance at p<0.05. Baseline characteristics of all randomised participants will be first summarised for each group using descriptive statistics. Continuous variables will be reported as numbers of observed and missing values, means and SD or medians and IQR, depending on their distributions. Categorical variables will be described as frequencies and percentages.

Analysis of covariance regression models will be used to evaluate the main treatment effects on the primary outcome at each scheduled visit, adjusting for important baseline confounding variables (if any). Model-estimated means will be presented for each group, and their differences will be tested. A repeated measures analysis will be conducted as a secondary approach in order to investigate changes over time. This will utilise participant data collected at the multiple visits. Sensitivity analyses will be considered on the primary outcome with missing data, using multiple imputations and/or other prespecified imputation methods when deemed appropriate (ie, data missing at random). A similar approach will be applied to other continuous secondary outcomes. Generalised linear models will be used for categorical outcomes, using specific link functions.

**Data monitoring**

A trial data safety and monitoring committee has been convened for this study. All members are independent of the study team. This committee will oversee all ethical and safety issues in accordance with current regulations and the Terms of Reference for the group. The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, in the interests of safety, or any other administrative reasons. The Sponsor shall take advice from the data and safety monitoring committee as appropriate in making this decision.

**Potential complications/side effects**

CML as a source of GA and phospholipids are a natural component of milk and found in the MFGM surrounding milk fat globules. The milk powder and other ingredients used in the formulation of our study products have been studied previously in both animal models and human studies (e.g. in infants) and in non-pregnant and pregnant women in New Zealand, Singapore and Indonesia, and are now commercially available. There is no known risk to human participants from any of these ingredients.

For the purpose of this study, an ‘adverse event’ (AE) includes any condition detected or diagnosed after the intervention has been administered and has a possible, probable or definite causal relationship with the intervention. A ‘serious adverse event’ is an AE as defined above that occurs after having received the intervention, and which results in a life-threatening outcome.
disability, incapacity or death. All AEs will be assessed for seriousness by the treating physician. Those events that are considered to be serious will also be assessed in order to identify causality. All serious AEs will be recorded and monitored until either resolution, stabilisation or until it has been shown that the study intervention is not the cause. They will also be recorded and reported to the relevant authority and research ethics committee as part of the annual reports. Serious adverse reactions will also be reported to the sponsor immediately.

**Auditing**

Forterra Co-operative Group Ltd, New Zealand, or its delegate will carry out regular monitoring and auditing to ensure that all procedures are being adhered to, subject information and all data collection systems are robust, there is appropriate recording of and responses to adverse events and furthermore, that sample handling, processing and storage are correct according to the standard operating procedures.

**ETHICS AND DISSEMINATION**

This project was approved by the Ethics Committee of Chongqing Medical University (Ethic No. 2014034). The whole study will be conducted in accordance with the recommendations set out for physicians involved in research on human participants, adopted by the 18th World Medical Assembly, Helsinki 1964. The trial will adhere to the principles of the International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP) and in accordance with all applicable regulatory requirements. The written informed consent, which authorises us to enrol the mother and her offspring into our study, will be signed and dated by each participant before they enter the trial. One copy of the consent will be kept by the participant and the other will be kept by the investigator. Any findings from the CLIMB study will be submitted to peer-review journals.

**Confidentiality**

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be ensured by assigning each subject a unique study number throughout the study. All computer entry and networking programmes will be done with coded numbers only. Medical information may be given to the participant’s medical team and all appropriate medical personnel responsible for the participant’s welfare. Clinical information will not otherwise be released without written permission of the subject. Participants will not be identifiable by name or personal details on any report forms or published material.

**Access to data**

After data collection is complete, the database will be locked, after which time no amendments will be possible. Thereafter, data will only be available to the investigators for statistical analysis. Data will, however, be made available for inspection on request by the participating physicians, the research ethics committee and the regulatory authorities.

**Protocol amendments**

Any protocol amendments will be reported, reviewed and initially approved by the study investigators and sponsor. These amendments will then be submitted to the Ethics Committee of Chongqing Medical University for approval. Participants will be informed of any protocol amendments. If a participant becomes dissatisfied with any protocol amendment, they are free to withdraw from the study at any time and without any impact on future medical care.

**DISCUSSION**

The CLIMB study aims to contribute novel data regarding the efficacy of supplementing pregnant women with CML. In particular, we hope to generate original findings regarding its effect on maternal/infant lipid levels and on infant cognitive development. Studies of CML and GA are well described, but to the authors’ knowledge, their potential effects on infant outcomes in humans (particularly when supplemented during pregnancy), has never been investigated. With the specifically formulated maternal milk product, we will assess the efficacy of prenatal GA supplementation for improving maternal complex lipid status and subsequent offspring neurodevelopmental outcomes.

Product A is a low-fat milk product containing low levels of CML, whereas product B contains restored levels of CML to match the levels found naturally in full-fat milk. We therefore hope to not only elucidate the most beneficial concentration of CML for the supplementation of pregnant women, but furthermore, observe a dose-response association between GA supplementation and maternal and infant outcomes.

In conclusion, we hypothesise that prenatal maternal supplementation of GA may improve brain development in the offspring. If favorable results for infant cognitive outcomes are observed in those supplemented prenatally, this (pregnancy supplementation) would represent an innovative mechanism via which offspring neurodevelopment may be improved and as such, may also serve to reduce the risk of congenital brain defects. This could be especially valuable in woman presenting in early pregnancy with an increased risk of delivering an infant with neurodevelopmental problems.

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Acknowledgements The authors would like to thank the First Affiliated Hospital of Chongqing Medical University and the Chongqing Health Center for Women and Children for providing sites for implementation of the study and allowing access to the medical data of participants. Professor Carlo Agostoni (Università degli Studi di Milano, Italy), Professor Robert Gibson (University of Adelaide, Australia), Professor John Colombo (University of Kansas, USA); Professor Sally D Poppitt (who holds the Fonterra Chair in Human Nutrition at the University of Auckland, New Zealand) and Barbara Kuhn-Sherlock (statistician consultant, New Zealand) are acknowledged for their review of the protocol. Dr Paul McJarrow and Rebecca Cann (Fonterra employees) are acknowledged for their review of the protocol and manuscript and contribution to the study concept. Dr Sophie Gallier (Fonterra employee) is acknowledged for her review of the manuscript and as the sponsor's project manager. Financial support for the study was provided by the New Zealand Primary Growth Partnership postfarm gate dairy programme, funded by Fonterra Co-operative Group Ltd, New Zealand and the New Zealand Ministry for Primary Industries.

Contributors SH wrote the first draft, reviewed and revised the manuscript; TM was integrally involved in the implementation of the protocol, contributed to the discussion section, reviewed the manuscript and provided important revisions; TN reviewed and revised the manuscript and provided essential intellectual content; SS was integrally involved in the implementation and data collection of the CLIMB study, reviewed the manuscript and provided important feedback; TZ was involved in the implementation of the protocol, reviewed the manuscript and provided revisions; TLH participated in data collection; AR contributed to the conceptualisation and design of the protocol; YYX was integrally involved in the conceptualisation, design and implementation of the protocol, provided critical revisions of the manuscript and is the project manager of the CLIMB Study; HZ is the co-investigator for CLIMB study and PNB and HBQ are the principal investigators.

Funding This work was supported by the New Zealand Primary Growth Partnership postfarm gate dairy programme, funded by Fonterra Co-operative Group Ltd, New Zealand and the New Zealand Ministry for Primary Industries. The design and conception of the study was led by the principal investigators and the research team in China. These individuals will direct the ongoing management of the trial, the analysis of data and the dissemination of study findings.

Competing interests AR is employed by Fonterra Co-operative Group Ltd, New Zealand.

Ethics approval This project was approved by the Ethics Committee of Chongqing Medical University (Ethic No. 2014034).

Provenance and peer review Not commissioned; externally peer reviewed.

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*BMJ Open* 2017 7:
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