The Effect of An Educational Program for Pregnant Women to Prevent Allergic Diseases In Infants: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background Allergic diseases in infants have dramatically increased in developed countries during the past few decades. To date, extensive research has been done on risk factors for allergies in infancy, and preventive measures against it. However, the effect of the primary approach to preventing infants’ allergy still remains limited. The aim of this trial is to evaluate whether prenatal education interventions, including the latest public research results on allergic diseases, prevent the infant allergies onset.

Methods/Design

We designed a randomized, controlled, two-arm (standard prenatal education vs our education), parallel-group, assessor-blind, trial. A sample of 120 pregnant women will be recruited at Chiba Aiyukai Kinen hospital and allocation is by computer-generated randomization. Pregnant women in the intervention arm participate in the childbirth education program established by the specialist and a pediatric allergy educator. The program was developed based on evidences supporting interventions on primary prevention, which are suggested to be beneficial to infant’s allergies in recent studies. The primary objective of the study is to determine whether it is possible to establish effective behaviors for allergy prevention during early infancy in pregnant women who participate in an educational program developed by pediatric allergy specialists. Four months after birth, their behaviors will be compared against those of pregnant women who did not participate in the program. Discussion Allergies are common in many individuals worldwide, and can be present from babyhood through the person’s lifetime. One of the strong points of this study is that it will provide pregnant women with accumulated information on preventive knowledge against allergy that can be effective in some cases, and women can apply a combination of these behavior before and after pregnancy. The results of our program will be publicized to help change the behaviors of mothers, and if the program is effective for preventing allergies in infants, it will be disclosed worldwide as a new preventive measure for allergy in infants.

Introduction

In Japan, as in most developed countries, the prevalence of allergy among infants, including atopic dermatitis (AD), food allergy (FA), asthma, and allergic rhinitis, has increased in recent years and is a serious health problem. The “allergic march,” which was first proposed by Minoru Baba and refers to the chain reaction of allergies in people predisposed to atopic dermatitis, has attracted a great deal of attention in recent years, and it has been suggested that preventative measures during the neonatal and early infancy period would be effective against this condition.

To date, extensive research has been conducted on the risk factors for, and preventative measures against, allergy during infancy. In addition, evidence supporting the efficacy of several of these preventative measures has accumulated. For example, in 2008, Lack hypothesized that sensitization to allergen occurs through environmental exposure to allergen through the skin and that consumption of food allergen induces oral tolerance (dual allergen exposure hypothesis), and proposed a new allergy prevention strategy based on the maintenance of skin barrier function. To verify the dual allergen exposure hypothesis, randomized clinical trials (RCTs) of the effects of a moisturizer were conducted, and its efficacy in AD patients was demonstrated. Lowe et al. (2016) performed a meta-analysis and
showed that a moisturizer can statistically significantly prevent infantile AD when used in the neonatal period, and that the onset of AD is associated with sensitization to egg white antigen. On the other hand, this analysis suggested that the efficacy of moisturizer alone used from the neonatal period is poor because it cannot prevent sensitization to food allergens.

In addition to the dual allergen exposure hypothesis, studies suggest that maternal intestinal bacterial flora is associated with neonatal allergy\(^{(10), (11)}\). Currently, probiotics\(^{(12)}\), prebiotics\(^{(13)}\), and synbiotics\(^{(14)}\) are effective for the treatment of abnormal intestinal bacterial flora. RCTs have examined the effects of probiotic intake by pregnant and lactating women on preventing the development of allergies in infants\(^{(15), (16), (17), (18), (19)}\). Zuccotti et al. (2015)\(^{(20), (21)}\) performed a meta-analysis on these RCTs, and suggested that probiotic intake in pregnant and lactating women can reduce incidence of rash in neonates. However, probiotics did not reduce the prevalence of asthma or allergic rhinitis. A different meta-analysis of RCTs assessing the effects of prebiotics\(^{(22)}\) and synbiotics\(^{(23)}\) showed that although these organisms prevent the development of rash, they have no protective effects against allergic sensitization in neonates. Additional studies are needed to assess the differences in intestinal bacterial flora between various races or regions.

Observational studies identified many risk factors and preventive measures for allergy in infants. An observational study that examined the association between living conditions and infantile asthma\(^{(24), (25)}\) reported that the combination of preventive measures to avoid allergens such as tick and mold can reduce the risk of allergy. Second-hand smoke from parents or other family members living together increases the risk of bronchial asthma in infants\(^{(26), (27), (28)}\). The association between living conditions and the risk of allergy in infants has been researched extensively. Many observational studies examined the correlation between food intake by pregnant women or lactating mothers and the development of allergies in infants. Specifically, the intake of vitamin D\(^{(29), (30), (31)}\) and n-3 polyunsaturated fatty acids\(^{(32), (33), (34)}\) during pregnancy reduces the risk of allergy in infants. However, there are no recent meta-analyses\(^{(35), (36), (37), (38), (39), (40)}\) or RCTs\(^{(41), (42), (43), (44), (45), (46)}\) demonstrating the efficacy of these nutrients against allergies.

The preventive measures reported to date have shown limited effects, and a clear and effective method to prevent allergies in infants remains to be identified. Because multiple risk factors are associated with allergies in infants, the preventive measures identified to date are not effective.

We hypothesized that providing pregnant women with knowledge regarding the latest research findings on allergy prevention in prenatal and postnatal period may increase awareness and knowledge and, thereby lead to changes in behavior to prevent allergy in infants. The aim of this trial is therefore to evaluate whether prenatal education interventions, including the latest public research results on allergic diseases, prevent the infant allergies onset.

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline. This report is based on protocol version 9, approved on March 1, 2019, by Chiba Aiyu-kai Kinen hospital Ethics Committee.
Methods

Objectives

Primary Objective

The primary objective of the study is to determine whether it is possible to establish effective behaviors for allergy prevention during early infancy in pregnant women who participate in an educational program developed by pediatric allergy specialists. Four months after birth, their behaviors will be compared against those of pregnant women who did not participate in the program.

Secondary Objectives

The secondary objectives are as follows:

▪ To determine whether the use of a moisturizer can reduce the onset of AD and eczema
▪ To determine whether the onset of other atopic disorders can be prevented by the use of a moisturizer.
▪ To examine the association between the onset of AD and food allergy sensitization.
▪ To establish the safety of the recommended moisturizer in neonates.
▪ To investigate the presence of allergies, skin condition, serum IgE, and TARC levels in neonates.

Trial design

This study is an assessor-blinded, randomized, controlled, parallel-group comparison study (comparing our educational program group with an established childbirth education group) conducted in Chiba Aiyukai Kinen Hospital (hereafter referred to as “our hospital”) to examine the superiority of the educational program over established programs. Subjects are randomized in a 1:1 ratio into one of the two groups. The participants and study personnel are not blinded with respect to the assignments.

This protocol is written in accordance with the Standard Protocol Item: Recommendations for Intervventional Trials (SPIRITS) guideline. Trial registration is through UMIN-CTR (R000038455).

Participants

Recruitment procedure
Participants are recruited among all pregnant women who visit our hospital for consultation regarding delivery. The investigator meets with each pregnant woman to provide oral and written information on the study and to request participation. Participants are selected according to the eligibility criteria. The pregnant women discuss participation with their respective families, and those who agree to participate in the study provide informed consent. After the collection of consent forms, the participants are randomized to one of two groups.

Eligibility criteria

Eligibility and exclusion criteria are as follows:

**Eligibility criteria (individuals must meet two criteria):**

- Those planning to give birth in our hospital
- Those planning to attend the childbirth education program provided by our hospital

**Exclusion criteria (any of the following criteria):**

- Those who were not planning to give birth in our hospital
- Those who did not attend our childbirth education program
- Neonates younger than 36 weeks
- Low birth weight (<2000 g)
- Birth to triplets or more
- Children with serious congenital malformations
- Abnormal birth including fetal distress and neonatal asphyxia
- Other pregnant women and neonates assessed as inadequate for the study by a doctor

Intervention

Intervention arm

Pregnant women in the intervention arm participate in the childbirth education program established by the specialist and a pediatric allergy educator. The program was developed based on evidences supporting interventions on primary prevention, which are suggested to be beneficial to infant’s allergies in recent studies. In this program, we propose three types of barriers that protect infants from allergy: the intestinal mucosa, respiratory tract mucosa, and skin. We then recommend behaviors for mothers that improve the
functions of these three types of barriers. Table 1 explains the details of the program using TIDieR\textsuperscript{47}, a template for intervention description.

**Control arm**

A leaflet summarizing the content of the educational program that is provided to the intervention arm is made available to subjects in the control arm at approximately 20 and 30 weeks of pregnancy.

**Measurements / Assessments**

**Primary outcomes**

**Self-evaluation of questionnaire to identify the behavioral characteristics of mothers based on the educational program at 4 months after delivery**

Primary outcomes are evaluated according to a self-evaluation score at 4 months after delivery in both arms. The score is determined using a survey sheet created for this study (Appendix 1) to assess the behavioral characteristics of mothers. We prepared 21 questions to assess the dietary habits of mothers, living conditions, and the skin care of children based on the ideal behavior of mothers to prevent allergy in infants as proposed by specialists. Five options (a–e) are provided for all questions: a=1, b=2, c=3, d=4, and e=5. Higher scores indicate more appropriate behaviors of mothers to prevent pediatric allergy at each time point.

**Secondary outcomes**

We set the following seven secondary outcomes:

1. **Incidence and severity of atopic dermatitis and eczema infantile**

   The incidence and severity of AD and eczema in infants aged 1 week, 1 month, 4 months, and 12 months are determined by a blinded pediatrician according to the Clinical Practice Guidelines for the Management of Atopic Dermatitis 2016 prepared by the Japanese Dermatological Association:

   URL: https://www.dermatol.or.jp/uploads/uploads/files/guideline/atopicdermatitis_guideline.pdf

2. **Incidence of food allergy and sensitization to egg white, milk, and ovomucoid**

   The incidence of food allergy in infants aged 4 and 12 months is determined by sensitization using serum antigen-specific IgE \textsuperscript{49}, medical interview, and oral food challenge or a clear history of allergy triggered by
accidentally ingested foods.

3. Analysis of stratum corneum hydration, transepidermal water loss, and microscopic and digital images

Stratum corneum hydration in infants is measured 3–5 times on the left lower leg, forehead, and left cheek using Skicon-200EX® (IBS Japan Co., Ltd, Shizuoka, Japan). Transepidermal water loss (TEWL) is determined 2–3 times on the left lower leg, forehead, and left cheek using the VapoMeter® (DelfinTechnologies, Kuopio, Finland). Enlarged images of the skin of the left lower leg, forehead, and left cheek in infants are acquired using a USB microscope M3 (Scalar Corporation, Tokyo, Japan). Images of a wide range of skin surfaces in infants are obtained using a digital camera (Canon Tokyo, Japan). The skin is measured and photographed at 22°C and 50% humidity.

4. TARC level

Serum TARC level is measured in infants aged 4 and 12 months to assess the severity of AD.

5. Frequency of use and amount of moisturizer

The total amount of moisturizer used during the study is calculated to predict the effect of the educational program. The moisturizer is provided free of charge to those who want to use it.

6. Questionnaire survey on living habits, awareness, and knowledge of mothers before and after pregnancy

A questionnaire survey on living habits, awareness, and knowledge of mothers before and after pregnancy was prepared before and after pregnancy, how they intend to provide nourishment for the baby, and their concerns regarding childcare and the skin care of the baby.

7. Adverse events

Self-reported adverse events associated with the use of the moisturizer provided free of charge to those who want to use it during the study are recorded.

Baseline characteristics

The baseline characteristics are evaluated at approximately 20 weeks of pregnancy. The variables to be measured include age; delivery experience; history and type of allergy of the subject, their partner, and siblings; type of pet, if any; and smoking status of the subject and her family members living together.
Participant timeline

Table 2 shows the consent forms obtained from the subjects, intervention, and evaluation schedule.

Sample size

In this study, the number of deliveries per month at the investigational site was estimated at 15–20, and at most 120 participants are expected over the course of the 1-year study. A questionnaire aimed at identifying the behavioral characteristics of mothers was created for the study to assess primary outcomes. Currently, there are no data showing the effectiveness of the survey sheet. Considering the inclusion of 60 subjects per group with a significance level of 0.05 and a standard deviation of 16 under the conditions described above, the expected upper limit of the standard error of the mean was approximately 8 using a \( t \)-test with a statistical power of 80%. Based on this estimate, the final target sample size was set at 120 patients. The statistical power was calculated using R ver.3.5.2 statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Randomization procedure and concealment of allocation

Participants who meet the eligibility criteria and agree to participate in the study are randomized after signing the informed consent form. These subjects are stratified according to the estimated delivery date into winter and other seasons, and randomized using the permuted block method. A statistical analyst generates a random allocation code using R statistical software (R Foundation for Statistical Computing) to randomize the subjects at each investigational site. The study is an assessor-blinded trial, and all raters are blinded with respect to the assignments. Also only the statistical analyst is aware of the stratification block size; the remaining staff is blinded. Subjects are randomized in a 1:1 ratio into one of two groups.

Statistical analysis

Full analysis set

Subjects enrolled in the study who started any of the study procedures are included in the full analysis set (FAS). However, those with a confirmed serious deviation from the protocol and those determined ineligible for the study after enrollment are excluded from the FAS.

Intention-to-treat analysis

In general, all statistical analyses are performed by the intention-to-treat principle.
Primary outcomes

Self-evaluation of questionnaire to identify the behavioral characteristics of mothers based on the educational program at 4 months after delivery

A linear mixed-effects model is used to analyze the total score of the questionnaire at 1, 4, and 12 months after delivery as an outcome variable. A mixed-effects model for repeated measurements (MMRM) is used to properly handle missing values or dropouts that could arise during the study. An unstructured covariance structure is used to assess the correlation between outcomes at these time points. Mean changes from baseline are modeled as outcome variables for the MMRM. Mean changes from baseline at each time point are analyzed individually using a regression model. If the regression parameters cannot be estimated using the unstructured model, the covariance structure is changed in the following sequence: Toeplitz matrix model, heterogeneous compound symmetry model, autoregressive model (1), compound symmetry model, and variance components model. A primary analysis is performed using estimates for the regression parameter or regression parameter test at 4 months after delivery. The significance level is set at 5% (two-sided).

Secondary outcomes

1. Incidence and severity of atopic dermatitis and eczema infantile

The incidence of infantile AD and eczema infantile is compared between groups at all time points using Pearson's chi-squared test. The severity of these diseases is compared between groups using descriptive statistics of scores at each time point. Subgroup analyses are performed to assess the incidence and severity of AD related to the amount and frequency of moisturizer used during the study and the skin condition of infants.

2. Incidence of food allergy and sensitization to egg white, milk, and ovomucoid

The rate of sensitization to each allergen is compared between groups with a cut-off value of the incidence of food allergy and the serum antigen-specific IgE level (equal to or more than class II) in infants at each time point using Pearson's chi-squared test. Subgroup analysis is performed to assess the outcomes related to the amount and frequency of moisturizer used during the study and the onset of AD in infants.

3. Analysis of stratum corneum hydration, transepidermal water loss, and microscopic and digital images

Descriptive statistics of the stratum corneum hydration, TEWL in infants and rate of changes in the score at each time point are calculated and compared between groups. Subgroup analysis is performed to assess the amount and frequency of moisturizer used in infants during the study. In addition,
exploratory investigation is performed to evaluate the skin images.

4. TARC level

Descriptive statistics of the serum TARC level at each time point are calculated and compared between groups. Subgroup analysis is performed to assess the incidence of infantile AD and eczema infantile, and the amount and frequency of moisturizer used during the study.

5. Frequency of use and amount of moisturizer

Descriptive statistics of the total amount of moisturizer and rate of changes in the scores at each time point are calculated and compared between groups. An evaluation is performed considering birth month as a baseline characteristic.

6. Questionnaire survey on living habits, awareness, and knowledge of mothers before and after pregnancy

Descriptive statistics of a questionnaire survey’s scores at each time point are calculated and compared between groups. Changes in the self-evaluation at each time point and the related factors are compared between groups.

Interim analysis

No interim analysis will be conducted.

Data collection procedure

All data will be analyzed by members specifically trained in the study protocol in our hospital.

Dissemination

Research ethics approval

The study will be performed according to the Declaration of Helsinki (adopted by the 18th World Medical Association General Assembly, 1964, including subsequent revisions) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare No. 3 of December, 2014). This study was approved by our hospital ethics committee.

Protocol amendments

Any amendments to the protocol will be submitted to the ethics committee of Chiba Aiyu-kai Kinen hospital for approval. Once approved, they will be reported to all the study investigators and, when
necessary, to the study participants.

Confidentiality

All personnel involved in this study shall comply with the applicable laws and regulations regarding confidentiality. Study personnel must make every effort to protect confidential information on the subjects and must not disclose the information obtained during the study to any third party without due cause. This is binding for any personnel even after they are no longer directly associated with the study. The investigator, the person in charge of the study, and study collaborators shall use subject identification codes or registration numbers to enroll subjects and prepare case report forms instead of personal information that could be identified by a third party such as name, initials, address, telephone number, or medical chart number. With respect to information disclosure, the investigator or other personnel must carefully handle study data on the subjects to ensure that the data are not disclosed.

Research funding and conflicts of interest

The authors declare no conflicts of interest related to the plan, implementation, and reporting of the study results and interpretation of the results. Researchers independently planned and will conduct this study without funding or benefits from a company. Subjects do not lose any right or benefit by participating in this study.

Safety of subjects and compensation related to participation in the study

Subjects will need to allocate a certain amount of time to the study as follows: approximately 180 minutes for participation in sessions at 20 and 30 weeks of pregnancy, approximately 30 minutes for completing the questionnaire survey, and approximately 30 minutes for skin measurements at each time point. No special compensation is paid because adverse health effects are not expected, as the aim of the study is to educate subjects. However, if subjects experience any abnormal feelings during blood collection in the study, they must promptly contact the investigator to receive proper treatment.

Dissemination policy

The full protocol will be published in an academic journal in English. The study results will be announced to the public through presentations in academic meetings and publications in academic journals.

Discussion
Allergy is one of the most important health issues in developed countries. Allergies are common in many individuals worldwide, and can be present from babyhood through the person's lifetime. Many observational studies and RCTs have been performed to address the prevalence of allergies. These studies revealed that specific intervention strategies to prevent allergies are effective in some cases.

One of the strong points of this study is that it will provide pregnant women with accumulated information on preventive knowledge against allergy that can be effective in some cases, and women can apply a combination of these behaviors before and after pregnancy. However, one limitation of this study is that it may not provide clear data on the association between individual preventive measures and risk factors for allergy because the mothers themselves will be responsible for selecting and applying a combination of preventive measures.

Currently, most pregnant women in Japan are concerned about the potential development of allergies in their babies. If the results of the study indicate that the educational program has a positive effect on preventing allergies, “prenatal education to prevent allergy in infants” should be added to the existing childbirth educational program provided by medical institutions and local governments or the doctor’s instructions provided during infant examinations. This may decrease the anxiety of pregnant women and prevent allergy in infants. Our educational program is based on research findings from papers published in international medical journals. Thus, this program, which is the first study to determine the effect of education on allergy prevention, is expected to be effective both within and outside the Japanese population. The results of our program will be publicized to help change the behaviors of mothers, and if the program is effective for preventing allergies in infants, it will be disclosed worldwide as a new preventive approach for allergy in infants.

**Trial Status**

Participant recruitment started in May 2019 and is scheduled to end in April 2020. This report is based on protocol version 9.

**Abbreviations**

AD : Atopic dermatitis

CI : Confidence interval

FA : Food allergy

PAE : Pediatric allergy educator

RCT : Randomized controlled trial

SCORAD : Scoring atopic dermatitis
TARC : Thymus and activation-regulated chemokine

UMIN-CTR : University hospital medical information network – clinical trials registry

VD : Vitamin D

**Declarations**

**Ethics approval and consent to participate**

The study will be performed according to the Declaration of Helsinki (adopted by the 18th World Medical Association General Assembly, 1964, including subsequent revisions) and the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and Ministry of Health, Labour and Welfare No. 3 of December, 2014). The study protocol was reviewed and approved by the ethics committee of Chiba Aiyu-kai Kinen hospital. All participants will provide written informed consent prior to participation.

**Competing interests**

All authors declare that they have no competing interests.

**Funding**

This trial is conducted with no external funding and is instead from internal funding.

**Consent for publication**

This item is not applicable.

**Availability of data and materials**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**Authors’ contributions**
YN and NI conceived of the study. RN wrote the first draft of the manuscript. All authors designed the study, and contributed to, read, and approved version of this manuscript.

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### Tables

Table 1 Details of the educational program provided to the intervention arm
| Item               | Description                                                                 |
|--------------------|-----------------------------------------------------------------------------|
| **1. Brief name**  | Perinatal education to prevent allergy in infants                           |
| **2. Why**         | Although many parents are anxious regarding allergies and skin conditions in infants, there are few opportunities to learn about the prevention of pediatric allergies and skin conditions. Extensive information on pediatric allergy is available based on scientific evidence, and prophylaxis in pregnant women is expected to be effective to prevent allergy in infants. If pregnant women learn how to prevent pediatric allergy based on scientific evidence and apply these principles to childcare, this can promote the establishment of a prophylactic strategy against allergy in infants. |
| **3. What materials** | Educational materials for the program were prepared using Power Point. A handbook with illustrations and photographs reviewed by a specialist is provided to mothers to educate them about proper skin care for infants and the optimal diet during pregnancy and lactation. |
| **4. What procedures** | A session planned during early and late pregnancy consists of the following:  
  Ø **Program in Early pregnancy**
    - Title: What you can do for your baby
    - Subtitle: Advice from pediatric allergy specialists.
    - **Intestinal mucosa**
      - Effect of the maternal intestinal bacterial flora on the fetus
      - A diet that includes nutrients (oligosaccharides, dietary fiber, and fermented food) is ideal for pregnant women to control intestinal bacterial flora
      - Effect of vitamin D and a diet that includes vitamin D.
      - Effect of n-3 polyunsaturated fatty acids and a diet that includes this acid
    - **Skin**
      - Association between the skin of infants and sensitization to allergens
      - Adequate exposure to ultraviolet light
    - **Respiratory tract mucosa**
      - Effect of smoking on pediatric bronchial asthma  
  Ø **Program in Late pregnancy**
    - Title: What you want to know for your baby?
    - Subtitle: Advice from specialists on pediatric allergy: “Three barriers protecting our body” |
Intestinal mucosa

(The same content as in Program in Early pregnancy)

Skin

ü Association between the skin of infants and sensitization to allergens

ü Differences between the skin of infants and that of adults

ü Prevention of allergic dermatitis and proper skin care starting at the neonatal period

ü Proper skin care for neonates (how to wash and moisturize the skin)

ü Proper exposure to air

Respiratory tract mucosa

ü Effect of smoking on pediatric bronchial asthma

ü Risk of exposure of infants to allergens in the living environment, in particular in bedclothes

ü Cleaning bedclothes and the living areas of infants

|   |   |   |
|---|---|---|
| 5. Who provides | Specialist or educator of pediatric allergy |
| 6. How | Face-to-face group learning |
| 7. Where | Chiba Aiyukai Kinen Hospital where pregnant women are planning to give birth |
| 8. When | Two 90-minute sessions (at approximately 20 and 30 weeks of pregnancy) |
| 9. Tailoring | Not individualized |
| 10. Modification | Any changes occurring during the study period need to be reported. |
| 11. How well | Plan: To promote adherence to the recommended skin care practices among subjects participating in the educational program. A moisturizer is provided free of charge to those who want to use it. |
| 12. How well | Practice: Strategies to promote adherence to skin care practices will be reported in a paper. |

Table 2 Consent, enrolment/allocation, and assessment of subjects
| Study PERIOD | Enrolment / Allocation | Post-allocation |
|-------------|------------------------|-----------------|
| **TIME POINT** | Early pregnancy | 20 weeks of pregnancy | 30 weeks of pregnancy | Delivery | Discharge | 1 month after delivery | 4 months after delivery | 12 months after delivery |
| ENROLMENT / ALLOCATION: | | | | | | | | |
| Inclusion | ● | | | | | | | |
| Obtaining informed consent | ● | | | | | | | |
| Randomization | ● | | | | | | | |
| Baseline survey | | ● | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| Educational program | | ● | | | | | | |
| Established childbirth education | | | ● | | | | | |
| ASSESSMENTS: | | | | | | | | |
| Questionnaire survey on living habits, awareness, and knowledge of mothers before and after pregnancy | | ● | | | | | | |
| Survey on the behavioral characteristics of mothers | | ● | | | | | | |
| Blood collection from mothers | | ● | | | | | | |
| Blood collection from infants (IgE and TARC) | | | ● | | | | | |
| Stratum corneum hydration of infants | | ● | | | | | | |
| TEWL of infants | | ● | | | | | | |
| Findings on the skin of infants (scoring atopic dermatitis [SCORAD]) | | ● | | | | | | |
| Images of the skin of infants | | ● | | | | | | |
| Diagnosis of atopic dermatitis in infants | | | ● | | | | | |
| Diagnosis of food allergy in infants | | | | ● | | | | |
| Provision of moisturizer | | | | | ● | | | |
| Collection of the moisturizer | | | | | | ● | | |
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