RISK OF HYPOGLYCEMIA IN NEWBORNS FROM MOTHERS WITH GESTATIONAL DIABETES

FINAL DEGREE PROJECT

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1. SUMMARY.

There are not enough previous publications which are focused on mothers with well-controlled gestational diabetes mellitus (GDM) as a risk factor that determines the occurrence of neonatal hypoglycemia. In addition, approaches to blood glucose monitoring have been inconsistent and poorly defined. Our objective is to determine if being a newborn from a mother with well-controlled gestational diabetes (regardless insulin treatment) have a higher risk to develop hypoglycemia than a healthy newborn, using a defined and strict protocol. The project will take place in a regional hospital of Girona. We will recruit from 2014 to 2015 a cohort of 623 infants born in this center without any malformation or any perinatal pathology or complication, selected with a consecutive sampling. We will record sex, ethnicity and gestational age information. We will measure blood glucose levels and anthropometric measurements in newborns always taking into account the presence of well-controlled maternal gestational diabetes or not. Patients will be followed up during 24 hours to determine the incidence of hypoglycemia. We will analyze the contribution between exposure factors that we have studied and the incidence of the outcome using a multivariate analysis.

2. INTRODUCTION.

2.1 Epidemiology.

Hypoglycemia is the most common metabolic disorder of newborns, and glucose concentration is one of the most common biochemical measurement in the neonatal intensive care unit [18]. It has been estimated that 10% of normal term infants cannot maintain a plasma glucose concentration above 30 mg/dL if their first feeding is delayed 3-6 hours after birth [3]. The incidence of hypoglycemia is estimated to be 5%-15% in otherwise healthy babies [1], however, the incidence of hypoglycemia may increase from 3% to 29% when preterm newborns are included [13].

Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy. The incidence of GDM has increased over the last decades,

this is due to the increase of obesity, maternal type 2 diabetes mellitus and advanced maternal age [21]. GDM has a prevalence of 7.5%, and it is one of the metabolic disorders diagnosed in the mother that increase the risk of hypoglycemia in the newborns up to 27% compared to newborns of non diabetic mother and, particulary if the mother was not well-controlled during pregnancy. A study from Parc de Salut Mar (Barcelona) concluded that mild and moderate neonatal hypoglycemia were common in infants of women with GDM in the first day of live, although sever hypoglycemia is unusual and occurs early after birth [24]. Some studies have shown that the neurodevelopment outcome of infants of well-controlled diabetic mothers appears to be similar to that of normal infants. However, poorly controlled diabetes can produce development abnormalities in the offspring [7].

Macrosomia can occur in all diabetic pregnancies, but the incidence appears to be greater in infants born to mothers with pregestational diabetes. This is shown by the following studies: one of them based on a population of 3705 infants born to mothers with type 1 diabetes between 1998 and 2007 in Sweden, 47% of the infants were large for gestational age. In another study from Sweden based on all births in the Swedish Medical Birth Register from 1992 to 2004, infants born to mothers with gestational diabetes were four times more likely to be large for gestational age than infants born to nondiabetic mothers (15.8 versus 3.6%) [7].

Different risk factors exist to develope transient hypoglycemia in the neonatal period, which can be present during pregnancy, such as infants of mothers treated with beta adrenergic agents or infants of diabetic mothers (IDM) type I or II controlled with oral hypoglycemic agents, or infants of gestational diabetes mother. There are also factors that occur in the immediate postnatal period such as: prematurity, infants who are large (macrosoma) or small for gestational age (SGA), infants who require intensive care (eg, sepsis and asphyxia) or infants with polycythemia [3]. In a prospective study with 14168 newborns delivered in Tabriz Alzahra Hospital, where cases with blood glucose <50 mg/dL were considered as hypoglycemic newborns, prevalence of neonatal hypoglycemia was greater in: prematurity (61,5%), IDM (13,6%), septicemia (9,6%), perinatal asphyxia (9,6%), stress (3,8%) and neonatal hyperinsulinism

(1,9%) [11]. Some reports also have shown the presence of three or more risk factors may increase the severity of hypoglycemic episodes [19].

Another study has valuated the maternal ethnic differences in the incidence of neonatal hypoglycemia in babies born to gestational diabetic mother and conclude that there is higher risk of neonatal hypoglycemia in some ethnic groups, specially in Pakistani women [21]. However, a study from a multiethnic population of Barcelona has shown that neonates born to Latin American women with gestational diabetes had the highest prevalence of overall and moderate hypoglycemic events; but severe neonatal hypoglycemia was not statistically different among the five ethnic groups [23].

Other reports, such as Cole and Peevy in 1994 found that cesarean sections increase the risk of hypoglycemia, while a study of the American Journal of Obstetrics shows outcomes against this. In addition, another study demonstrated an increase in the risk of neonatal hypoglycemia when weight gain was above the recommendations of the Institute of Medicine [13].

2.2 Definition of hypoglycemia.

At present, it is difficult to define pathological neonatal hypoglycemia with an accurate value of glucose [22] and remains one of the most controversial issues in the scientific literature in the last decades [13]. No definition of pathologic hypoglycemia or guideline for treatment of low plasma glucose concentrations in newborns has been validated in clinical practice or assessed in prospective follow-up studies [1]. Koh and colleagues, in 1986 and 1992 performed a review of several pediatric textbooks and surveys of neonatal pediatricians to determine the threshold concentrations used to define hypoglycemia. In the first study, they identified definitions of hypoglycemia in term newborns ranging from 18 to 45 mg/dL from textbooks and 18 to 70 mg/dL from surveys. When both studies were compared, they showed that the median threshold concentration had increased significantly between 1986 and 1992. In 1992, most pediatricians considered a safe blood glucose concentration to be greater than 36 mg/dL [12]. In 2011, the American Academy of Pediatrics (APP) noted that the

generally adopted level used to define neonatal hypoglycemia was less than 47 mg/dL, and proposed an operational threshold of 45 mg/dL (2.5 mmol/L) as a target glucose level prior to routine feeds [3]. Other authors define hypoglycemia as blood glucose levels lower than 50 mg/dL, with a plasma glucose concentration of 60 mg/dL regarded as the lowest acceptable concentration during hypoglycemia treatment [8]. For this reason, there are so much controversial data on the epidemiology of neonatal hypoglycemia due to the lack of uniformity in glucose levels used to define hypoglycemia. Therefore, it is easy to understand the high variability in the described prevalences [21].

2.3 Problem statement.

Neonatal hypoglycemia is a serious condition that may lead to irreversible neurological damage with severe consequences [2] or even death if not treated promptly [13]. Severe hypoglycemia in the newborn is associated with selective neuronal necrosis in multiple brain regions [20]. Yet, it is not known how low, how often, or for how long low plasma glucose concentrations must occur before there is irreversible neuronal damage [3] or clinical manifestations develop [13]. It is important to note that neurological damage can be present even in asymptomatic newborns [13]. Preliminary long-term data has suggested residual defects in approximately 35% of symptomatic and 20% of asymptomatic infants [17].

The management of neonatal hypoglycemia is based on attempts to detect low glucose concentrations in newborns at risk and the maintenance of blood glucose concentrations higher than a safe level [18]. Previous publications show that babies in different risk groups have similar incidence of hypoglycemia, and episodes also occur at a similar time. This suggests that all babies at risk could be monitored using the same screening protocol, simplifying recommendations for clinical practice [19]. On the other hand, some authors had suggested that protocols should be individualized for each baby depending on the risk group, because the blood glucose measurement is invasive and painful and they did not consider it ethically correct to make this blood samples collections in otherwise well babies [19].

As newborns at risk of hypoglycemia are subjected to multiple painful pricks, another aspect to take into account is the consequences of pain or stress experiences. A review provides evidence that significant and long-lasting physiological consequences may follow painful insults during the neonatal period, including changes in the central nervous system and changes in the neuroendocrine and inmmune systems to stress at maturity [25].

2.4 Pathogenesis.

Glucose is the main source of energy for organ function. Although all organs can use glucose, the human brain uses it almost exclusively as a substrate for energetic metabolism [20]. In the majority of healthy newborns, the frequently observed hypoglycemia is not related to any important problem and only reflect normal processes of metabolic adaptation to extrauterine life [15]. During pregnancy, the fetus receives a continuous nutrient supply through the placenta controlled by maternal metabolism with a minimal need for fetal endocrine regulation [20]. At birth, when the transplacental glucose supply is abruptly interrupted, the newborn has to adapt to a new metabolic environment of enteral feeding with milk, alternated with fasting periods [2]. Most healthy newborns are able to quickly initiate glucose production to maintain adequate concentrations during the fasting periods to satisfy their energetic demands. This occurs by means of increased plasma catecholamines, glucagon, and cortisol, in combination with a decrease in plasma insulin concentrations that promote glycogenolysis, gluconeogenesis, lipolysis, fatty acid oxidation, and muscle protein breakdown. Altogether, the goal of neonatal glucose homeostasis is to provide the brain and other vital organs with sufficient glucose for energy [12].

Transient neonatal hypoglycemia is autolimited in the first 7 days after birth and it is a consequence of limited energetic reserves caused by excessive peripheral consumption, by an early depletion of energetic reserves or by an immaturity of the hypothalamic-pituitary system, responsible for the secretion of counterregulatory hormones [16].

Premature infants and those with intrauterine growth retardation (IUGR) are at risk of developing transient hypoglycemia. Preterm infants have limited glycogen reserves because glycogen storage takes place primarily during the third trimester. In addition to that, preterm infants and those who have IUGR also have decreased accumulation of protein and fat. As a result, their ability to maintain glucose production by glycogenolysis and gluconeogenesis for more than short periods of fasting is limited [12].

One of the most common causes of hypoglycemia in newborns linked to fetal hyperinsulinism is uncontrolled diabetes in the mother. These newborns tipically present symptomatic hypoglycemia within the first 4 to 6 hours after birth that is persistent, although other complications associated could modify the hypoglycemia onset. These neonates have an increased insulin production due to an increased sensivity of pancreatic beta cells to glucose, which can persists for days after birth [2]. Macrosomia is a common complication in infants born to diabetic mothers. These macrosomic newborns have a higher risk to develop hypoglycemia because of persistent hyperinsulinemia after the maternal glucose supply interrumption [7].

2.5 Clinical manifestations.

Neonatal hypoglycemia can present symptoms, such as lethargy, hypotonia, apnea, tachypnea, weak suck, poor feeding, weak cry, jitteriness, irritability, hypothermia, seizures or coma [2][3], the most common symptoms being apnea with cianosis and lethargy [13]. This clinical presentation is very inespecific and variable because many of these signs can result from other common neonatal disorders, including sepsis, hypocalcemia, hypothermia or intracranial hemorrhage [8]. However, neonatal hypoglycemia can be present in asymptomatic newborns, thus, this situation can aggravate the consequences because of a delayed diagnosis and treatment [3].

2.6 Justification.

The need to develop this study lies on the scarcity of previous publications regarding the risk of hypoglycemia in infants born to well-controlled gestational diabetic mothers. In addition, approaches to blood glucose monitoring have been inconsistent and poorly defined, and in many cases have used unrealiable screening methods to detect hypoglycemia. Furthermore, the study could provide a great benefit for newborns who in fact are not at risk or have a similar risk than a healthy newborn to develop hypoglycemia, preventing or reducing significantly the number of pricks. These blood glucose measurements are painful and can produce long-term sequelae in the newborn. On the other hand, a reduction of these interventions also involves some cost-savings for the national health system.

The technical capacity to achieve the project is optimal since all the measures can be taken in an easy, inmediate and economic way. A regional hospital is also available where the project can be comfortably carried out. All of this justify the proposal to analyze the contribution of well-controlled gestational diabetes as a risk factor in neonatal hypoglycemia.

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4. QUESTION.

Is the well-controlled maternal gestational diabetes (regardless insulin treatment) the factor that determines the occurrence of hypoglycemia in newborns?

5. HYPOTHESIS.

Neonates born to mothers with well-controlled gestational diabetes have the same risk than neonates whose mothers do not have gestational diabetes.

6. OBJECTIVES.

6.1 Primary objective: to determine whether newborns from a mother with well-controlled gestational diabetes (with or without insulin treatment) have a higher risk to develop hypoglycemia than healthy newborns.

6.2 Secondary objectives:

- To determine the incidence of hypoglycemia in infants born to mothers with well-controlled gestational diabetes.
- To determine the incidence of hypoglycemia in infants whose mothers do not have gestational diabetes.
- To calculate the Relative Risk (RR) of hypoglycemia in infants born to mothers with well-controlled gestational diabetes.
- To determine the number of newborns large for gestational age from mothers with well-controlled gestational diabetes.
- To determine the number of newborns small for gestational age from mothers with well-controlled gestational diabetes.
- To determine standard desviations of height and weight by gestational age of all newborns included in the study.

7. METHODS.

7.1 Study design.

Cohort study. Transversal, prospective, analytic and observational. We follow up the participants during 24 hours from the inclusion in the study.

7.2 Participants.

The study population will be all neonates born in a regional hospital in Girona between 2014 and 2015.

7.2.1 Inclusion criteria:

-Exposed group: healthy newborns from a well-controlled gestational diabetic mother (regardless insulin treatment) in the current pregnancy.

-Non-exposed group: healthy newborns from a mother without gestational diabetes.

7.2.2 Exclusion criteria:

-Newborns with malformations of any kind.

-Newborns with perinatal pathology like: respitatory distress, sepsis or metabolic diseases.

-Newborns who required resuscitation at birth.

-Newborns with loss of fetal wellbeing.

-Newborns who do not complete the IAS hypoglycemia protocol (Annex I).

-Infants born to mothers whose pregnancy was not well-controlled.

7.3 Sample selection.

A consecutive non-probability sampling will be taken. The sample recruitment will take part in a regional hospital in Girona for 2 years, we will take all the neonates born in this hospital. Parents of the potential participants will be invited to participate in the study by signing an informed consent (Annex IV). Nursing staff will take the capillary glucose samples according to the IAS protocol (Annex I).

7.4 Sample size.

Accepting an alpha risk of 0.05 and a beta risk less than 0.2 in a two-sided test, 567 exposed subjects and 56 in the non-exposed (623 in total) are necessary to recognize as statistically significant a relative risk greater than or equal to 2.5 if the rate of patients in the non-exposed group is 0.1. A drop out rate of 5% has been anticipated. The POISSON approximation. We have used the sample size and power calculator GRANMO. It is estimated that in the regional hospital in Girona we will have an approximate number of 2800 births during 2 years.

7.5 Variables.

All measures will take place in the same regional hospital where the participants are treated.

7.5.1 Dependent variable (outcome): neonatal hypoglycemia. It is defined when blood glucose levels measured on capillary blood samples are less than 45 mg/dL (2.5 mmol/L) [3] by the nursing staff using a glucometer. Samples will be taken at 1 hour after birth regardless of feeds, then before feeds at 2 and 3 hours after birth, then at 6 hours, at 12 and 24 hours. Always using the neonatal hypoglycemia screening protocol of the regional hospital (Annex I).

7.5.2 Independent variable: being born to a mother with gestational diabetes. It is defined as diabetes mellitus that is first detected during pregnancy [7]

through screening performed according to the protocol of the Gynecology and Obstetrics Service of the regional hospital.

7.5.3 Covariables:

- **Sex.**
- **Ethnicity**. 6 ethnic groups will be categorized: Caucasian, Latin American, Moroccan, Subsaharan, East Asian and South-Central Asian [23].
- **Gestational age.** It is determined by the first day of the woman's last normal menstrual period (LMP) and this is confirmed by obstetric ultrasound in the Department of Gynecology and Obstetrics of the regional hospital. We considerate a preterm infant if was born before 37 weeks gestational age [2].
- **Weight.** We will use a digital pediatric scale that will be calibrate each day, and after each measurement will be checked to return to zero. The measurement will be performed by a nurse with newborns in decubitus supine position and naked. We considerate small for gestational age neonates whose weight at birth are <2 SD (Standard Desviation) or <3P (third percentile) under mean for gestational age [4]; and large for gestational age or macrosomic neonates whose weight at birth is higher or equal than 97P (97th percentile) which is the equivalent to SD+2 (Standard Desviation) [9], based on data derived from adequate reference population, sex and gestational age (Annex IIa/b).
- **Height.** We will use a pediatric measuring board and the measurement will be performed by a nurse with newborns in decubitus supine position and naked, it is necessary to calculate the length between the top of the skull and heel with maximun extension of the lower limb.
- **SD (Standard Desviation):** it is estimated for weight and height based on the Anthropometric Growth Patterns by Dr. Carrascosa (Annex IIa/b).

7.6 Measure instruments.

-Ultrasound machine Toshiba Nemio XG

-Digital pediatric scale "Seca gmbh & Co.Kg". Modelo: 375 7021099

-Pediatric measuring board "Chorder". Ref: HM80D

-Glucometer "Stat Strip Xpress" TM. Ref: 4704 from "Nova Biomedical"

-Glucometer strips "Stat Strip Xpress". Ref: 42214 from "Nova Biomedical"

-Sterile metallic lancets from MenaLancet®

7.7 Methods of data collection.

Data will be collected directly from the medical records during the first days of postnatal period and will be reflected in database. Homogeneity in data collection must be ensured. The identification of the cohort will be performed by the same physician and the medical history will be checked daily to identify the group who meet the inclusion and exclusion criteria.

8. STATISTICAL ANALYSIS.

To analyze the contribution between exposure factors (confounding variables) that we have studied and the incidence of the outcome (hypoglycemia), a multivariate analysis will be performed using a logistic regression model.

9. ETHICAL ASPECTS.

This study is designed in accordance with the medical ethics requirements defined on the WMA Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (last revision in october 2013) and it has been approved by the Clinical Research Ethics Committee (CEIC) of the Hospital Santa Caterina. The information will be confidential, guaranteeing the

anonymity of the patients involved in the study under the Organic Law of Data Protection. In addition, parents of newborns will be informed about the interventions (Annex III) and they must sign an informed consent (Annex IV) before being included in the study.

10. STUDY LIMITATIONS AND BIASES.

One of the main problems of the study is the confounding bias because the cause-effect relationship is difficult to control due to covariables. This limitation will be minimized through a multivariate analysis. Another possible limitation could be the lost to follow up, however, in this study the lost will be minimun because the subjects included will be hospitalized during the 24 hours of the follow up.

11. WORK PLAN.

Researchers: Cynthia Morales (CM), Antonio Sánchez (AS). The study has been designed in 5 phases:

1. Coordination phase (2 months): Researchers: CM, AS. There will be organizational meetings of the research group with the nursing staff and the statistical consultant at the beginning of the project. The timeline of the study will be planned and the methods of data collection will be shared. Training of the nursing staff will take place in this period.

2. Patient recruitment (24 months): Researchers: CM, AS. The samples and variables of the patients will be collected at the beginning. It is estimated 730 days in 2 years. It is necessary to include 1 patient per day approximately to get to recruit the 623 participants needed in 24 months. The quality of the data will be checked regularly. With each patient: A) Start: consecutive samples will be taken from all the infants born in the hospital. B) Interview with parents: explanation of the purposes, questions about the check-ups during pregnancy and medical history of the parents, explanation of voluntary participation and signature of the informed consent. C) The nursing staff will perform capillary

glucose measurements according to protocol and weight and height will be calculated. D) To communicate our gratitude to the parents for their cooperation in the study.

3. Data extraction and processing data base (29 months): Researchers: CM, AS. Collection of information about weight, height and capillary blood glucose measurements. Measurement management: enter information in the database while the project is being developed. Regularly, an analysis of data will be performed to control its evolution.

4. Data analysis (9 months): Researchers: CM, AS. After the recruitment, all data collected will be analyzed and an analysis of the risk factors of the population will be done. Then, a multivariate analysis will be performed using logistic regression models to examine the contribution of confounding variables.

5. Interpretation of results, writing articles and dissemination of research findings (6 months). Researchers: CM, AS. An interpretation of the results will be performed and the corresponding articles will be written. In Annex V you can see the timeline.

12. DISSEMINATION PLAN.

The results of this study will be discussed and presented through conference presentations, meetings, training sessions, journal articles, reports and other documents. Further applicability studies would be necessary to recognize the worth of a possible change of protocol.

13. AVAILABLE MEANS TO CARRY OUT THE PROJECT:

The project will take place in a regional hospital in Girona. This center will provide rooms for the clinical examination of newborns and basic material such as office furniture and stretchers. The hospital has all the necessary items, including the informatic equipment suitable for processing databases for the project development without additional cost. However, the nursing staff and the

disposable items, such as: lancets, glucometer, strips, gloves, gauze sponges and alcohol used for capillary blood samples of the non-exposed group will be paid by the project.

14. BUDGET.

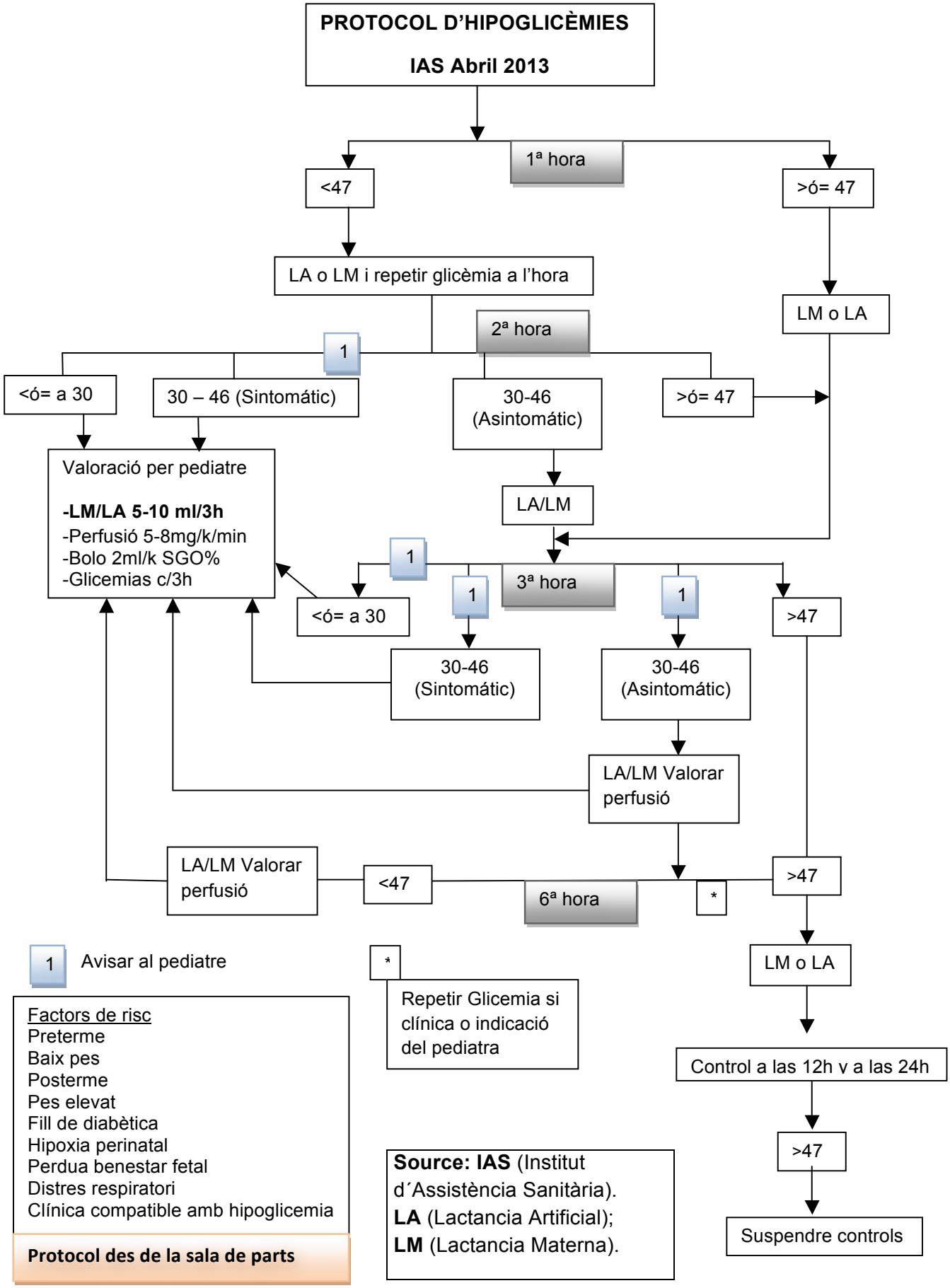
	CATEGORY	QUANTITY	TIME	COST
PERSONNEL COSTS	Nursing staff	3	24 months	7.200 €
	Statistical consulting and analysis for study data	1		2000 €
			SUBTOTAL	**9200** €

	ITEM	QUANTITY	DESCRIPTION	PRICE PER UNIT	COST
DISPOSABLE ITEMS	Glucometer strips	700 U	Box of 100	0,30 €	210€
	Metallic lancet	700 U	Box of 200	0,20 €	140 €
	Gauze sponges	700 U	Box of 200	0,033 €	23 €
	Alcohol	2 bottles	Bottle of 1L	2,40 €	4,8 €
	Latex gloves	700 U	Box of 100	0,06 €	42 €
				SUBTOTAL	419,8 €

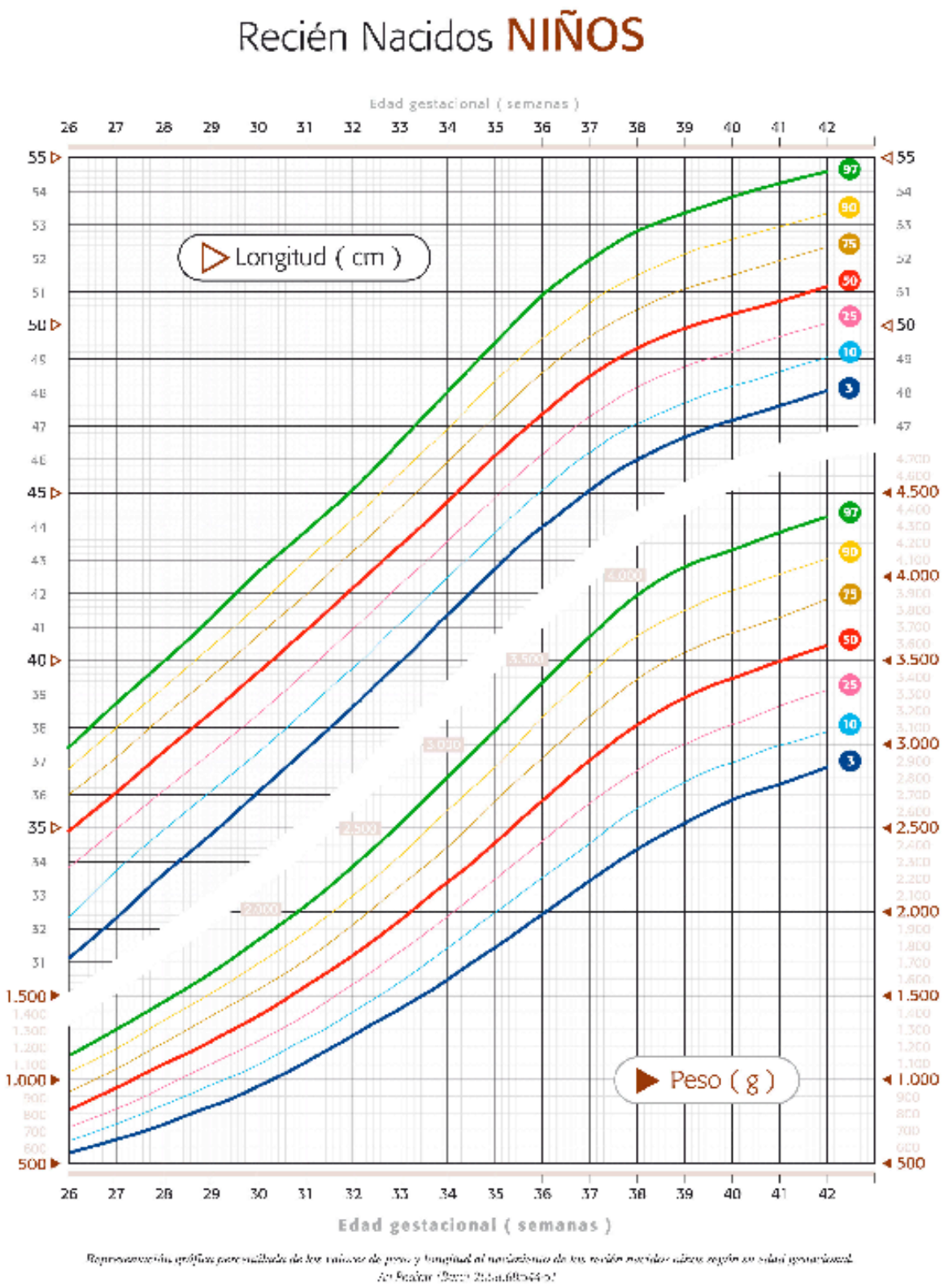
	ACTIVITY	COST
TRAVEL COSTS	Coordination meetings	600 €
	Investigator meetings	2500 €
	Study promotions	1000 €
		SUBTOTAL 4100 €

TOTAL AMOUNT OF AID CLAIMED	**13.719,8 €**

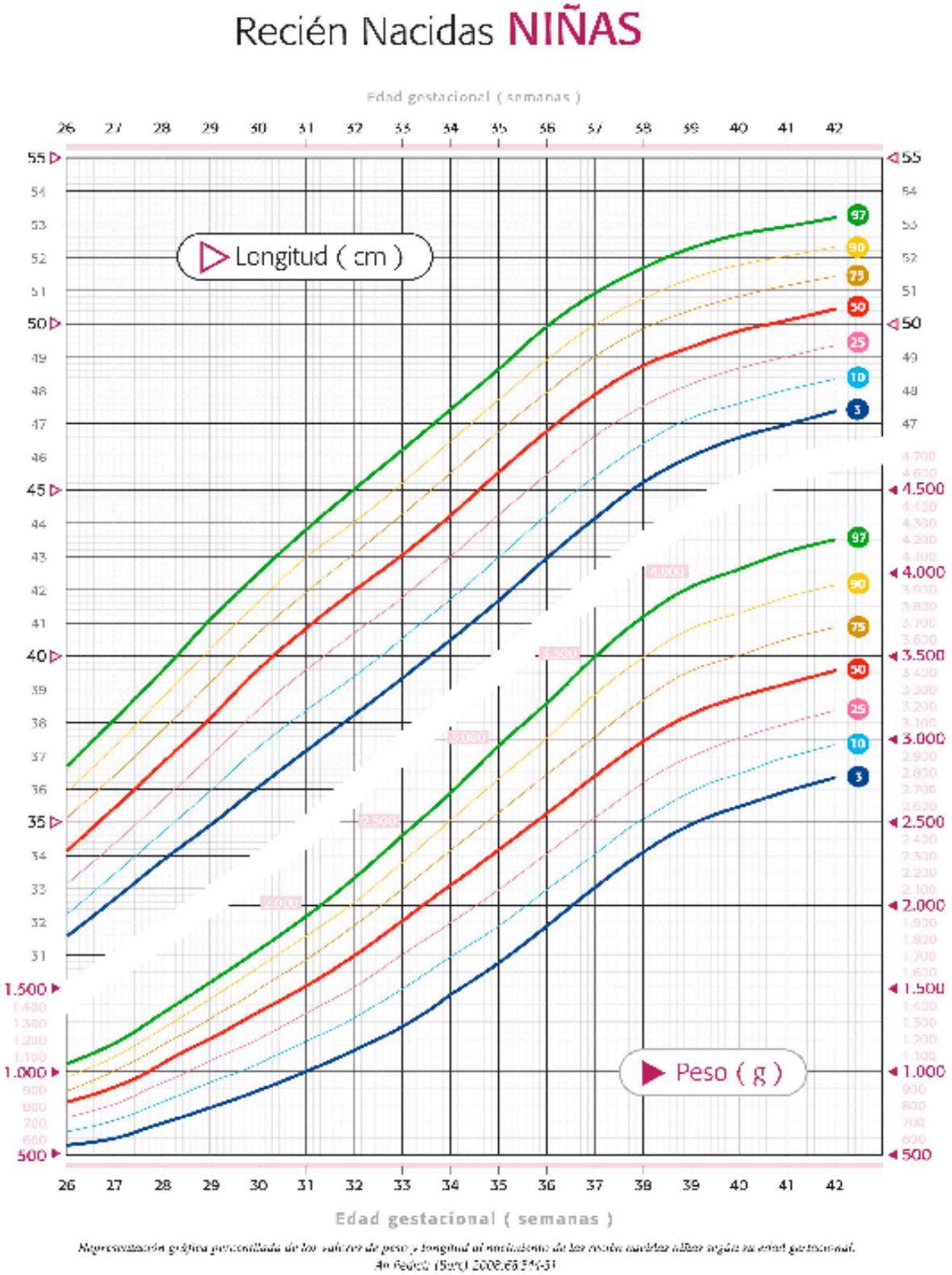
ANNEX I. IAS HYPOGLYCEMIA PROTOCOL



ANNEX IIa: ANTHROPOMETRIC GROWTH PATTERNS FOR BOYS



ANNEX IIb: ANTHROPOMETRIC GROWTH PATTERNS FOR GIRLS



Representación gráfica percentilada de los valores de peso y longitud al nacimiento de los recién nacidos niñas según su edad gestacional.
An Pediatr (Barc). 2008;68:544-51

ANNEX III: INFORMATION SHEET FOR PARTICIPANTS.

Project title: "Risk of hypoglycemia in newborns from mothers with gestational diabetes".

We appreciate your cooperation in this study. Your participation is contributing significantly to improving the knowledge about the risk factors that affect the decline of glucose/sugar (hypoglycemia) in newborns.

Purporse: We invite you to have your child participate in this research which main purpose is to study if maternal well-controlled gestational diabetes (diabetes diagnosed during pregnancy) is really a significant risk factor in the occurrence of hypoglycemia in the newborns.

Description of the process: During the participation of your child in the study we are going to inform about the objectives of the project and we are going to answer any question you may have. If you decide that your child is going to participate, you will be asked about some questions such as check-ups during pregnancy and medical records of the parents. An examination will be performed to your child which consists in take measures of weight and height and a small amount of blood will be taken from your child´s heel to measure blood glucose. Samples will be taken at 1 hour after birth regardless of feeds, then before feeds at 2 and 3 hours after birth, then at 6 hours, and finally at 12 and 24 hours.

The risk of taking these samples is minimal, although some complications can appear, such as mild infection or slight bruising, but these will desappear in a few days, and like any invasive procedure, your child will feel some discomfort. In addition, we will always use sterile equipment.

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to have your child participate or not. If you choose not to consent, all the services you and your child receive at this hospital will continue and nothing will change. You may also choose to change your mind later and stop participating, even if you agreed earlier, and the services you and/or your

child receives at the hospital will continue. You have the right to ask that any data you have supplied to that point be withdrawn or destroyed.

To contact with the researcher you can address to:

Cynthia Morales Álvarez

Servicio de Pediatría de Hospital de Santa Caterina

Carrer del Doctor Castany, s/n. Salt, Girona.

The information that we collect from this research project will be kept confidential in accordance with the Organic Law of Data Protection (Organic Law 15/1999) and the data will be used exclusively for the purposes of this project. Information about your child that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about your child will have a number on it instead of his/her name. Only the researchers will know what his/her number is and we will lock that information up, we will also respect the laws designed to protect biomedical research (14/2007) and any other that we can apply.

According to current legislation, you have the right to be informed about the important data about your child´s health that we get from the 24 hours of follow up of the study. This information will be shared with you if you wish, but if you prefer not to be informed, your decision will be respected.

To carry out this project and according to current legistlation, we ask for your consent. Before and after signing this document, if you have any questions you may ask them, even after the study has started. You will be given a copy of this information sheet.

ANNEX IV: INFORMED CONSENT.

Project title: "Risk of hypoglycemia in newborns from mothers with gestational diabetes".

Statement by participant:

I have read the foregoing information, or it has been read to me. I have been informed about the purpose and implications of this study, the process of collection, storage and processing of personal data; this data will be used exclusively for the purposes of this project. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I have understood that I can choose to change my mind later and stop participating and all services that I or my child receive at the hospital will continue without any consequence. I have been aware of the potential risks (if any). I consent voluntarily (without coercion) for my child to participate as a participant in this study.

Name of parent or guardian .....
.....

Name of participant .....
.....

Signature of parent or guardian .....

Date .....

Day/month/year

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the parent of the potential participant. I confirm that the parent was given an opportunity to ask questions about the study and all the questions asked by the parent have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this document has been provided to the participant.

Name of Researcher.....

.....

Signature of Researcher .....

Date .....

Day/month/year

REVOCATION OF CONSENT

Name of parent or guardian .....

.....revokes consent for participation in the study explained above.

Signature: ..... Date .....

Day/month/year

ANNEX IV: TIMELINE

ACTIVITY	PERSONNEL	NOV -DEC 2013	JAN-JUN 2014	JUL-DEC 2014	JAN-JUN 2015	JUL-DEC 2015	JAN-MAY 2016	JUN-SEP 2016	OCT-DEC 2016	JAN-MAR 2017
Coordination meetings	ALL THE TEAM									
Patient recruitment	CM, AS, NA									
Data extraction and processing database	CM, SC, AS									
Data analysis	CM, SC, AS									
Interpretation of results, publish and dissemination of research findings	CM, SC									

- CM (researcher): general coordination, economic management and publications.
- SC (statistical consultant): database control, data analysis, interpretation of results and publications.
- AS (pediatrician): discussion and interpretations of results and publications.
- NA (nursing staff): sample extractions and measurements.