Title Form

“Use of oral 40% destrogel to prevent hypoglycaemia in late-term births and SGA or LGA term newborns”

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Study Protocol

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Title of the study	**USE OF ORAL 40% DESTROGEL TO PREVENT HYPOGLYCAEMIA IN LATE-TERM BIRTHS AND SGA OR LGA TERM NEWBORNS**
Rational study	Neonatal hypoglycemia understood as a reduction in plasma glucose can result in long-term neurological damage. Hypoglycemia is one of the most frequent metabolic alterations of the newborn. About 30% of all newborns are at risk of hypoglycemia. The neonatal population at risk is mainly children of diabetic mothers, born prematurely, late preterm (34-36,6 weeks of gestational age), born at term (37-42 weeks of gestational age) with low body weight for gestational age (SGA, <10° percentile) or with high body weight for gestational age (LGA, >90° percentile) (1, 2, 3). The 50% of these infants have hypoglycemia in the first 48 years. It is still controversial today to assign the threshold value below which it is possible to define a condition of neonatal hypoglycemia. In 2011, the American Academy of Pediatrics provided practical guidance for screening and subsequent management of neonatal hypoglycemia in infants at risk. The chosen threshold was 45 mg/dl but they also stated that few studies have shown that the asymptomatic hypoglycaemia condition protracted for a few hours is associated with long-term neurological damage. Studies showing the correlation between plasma blood sugar concentration and long-term neurological adverse events were also influenced by the variable definition of hypoglycemia, the duration of hypoglycemia, the lack of studies case-control and sample size. The other chosen threshold to diagnose hypoglycemia was 47 mg/dl, however without rigorous scientific evidence (4). Subsequently in 2015 and 2017, two scientific evidence showed that maintaining blood sugar values above 47 mg/dl in the first 48 hours of life in infants at risk of hypoglycemia and in follow-up, did not associate with an increase in incidence of neurosensory type of alteration, at the age of 2 and 4.5 years of life respectively (2,5). Furthermore, these papers established the conditions of severe hypoglycemia for plasma glucose values <36 mg/dl and of recurrent hypoglycemia if at least three hypoglycemia episodes were recorded (<47 mg/dl) (5). The pathophysiological mechanisms underlying neonatal hypoglycemia were: the reduced glycogen storage in the liver of the preterm newborn, the reduced availability of amino acids for gluconeogenesis and the inadequate lipid storage as a source of fatty acids that are more evident in preterm. Regarding the causes of persistent hypoglycemia, specified as a hypoglycemia that persists more than 48 hours of life, we must consider: the inappropriate insulin secretion, hypopituitarism, cortisol deficiency, growth hormone deficiency, congenital errors of glucose metabolism, glycogen and fatty acids. Neonatal hypoglycemia can be completely asymptomatic or can manifest with neurogenic/adrenergic signs and symptoms. These are characterized by sweating, pallor, cyanosis, temperature instability, irritability, starvation, tremors, tachycardia and emesis. Neuroglycopenic signs and symptoms are characterized by apnea, hypotonia, hypovalid suction, seizures, coma and exitus (1).

	Serious monitoring of neonatal blood glucose is indicated in patients at risk of hypoglycemia. Glycaemic monitoring in the newborn at risk should be started not before of the two hours of life, in fact it is seen that at birth the neonatal blood glucose values are very low because they are conditioned by the metabolic activity of the foetus in the intrauterine phase, while later these values rise again until arrive at similar values to the adult within 48-72 hours (1). Monitoring is performed by glucometer, capillary EGA or blood sampling performed in patients at risk of painful stress (6). In recent years, various research groups have been evaluating the possibility of arriving at non-pharmacological prophylaxis of hypoglycemia. In particular, the Hegarty group has set up a protocol that uses dextrose gel at 40% in the risk categories that could reduce the number of hypoglycemia cases and consequently of painful procedures (7). Body temperature and the state of metabolic and/or respiratory acidosis are among the main factors that influence blood sugar levels in the first 48 hours of life (8,9). There are currently no strategies to prevent hypoglycemia. The treatment, in cases of asymptomatic hypoglycemia, is an early administration of milk in formula while in cases of symptomatic hypoglycemia infusion of 10% intravenous glucose is foreseen or early feeding by treatment with breast milk or in formula (10-14). However, the administration of milk formulated in the first hours of life causes a reduction in breastfeeding (10). In severe cases with glycaemia <36 mg/dl, it is practiced intravenous infusion of 10% glucose or dextrose (5). The 40% dextrose in gel administered orally can be a valid preventive measure in all newborns at risk of hypoglycemia, sons of a diabetic mother, SGA and LGA and improve the probability of successful breast attachment (7,12-16). Dextrose 40% in gel is administered by massaging into the buccal mucosa to have an optimal effect. In 2013 Harris et al. (14) conducted a study to evaluate the failure rate in the treatment of hypoglycaemia in a sample of 242 newborns assigned in the 1:1 ratio to case or control group. The cases were treated with 40% dextrose in gel with a concentration of 200 mg/kg while the controls with a placebo solution. Newborns of both groups were encouraged to feed but if the feeding was insufficient it was administered breast milk or formula milk through a syringe. Blood glucose was detected 30 minutes after gel administration but if hypoglycaemia was persistent, it was administered up to 6 doses of gel during the 48 hours of life. Treated group showed a failure rate in reversion of lower hypoglycaemia compared to controls (14% vs 24%, RR = 0.57 (0.33-0.98), p = 0.04). In 2016 Weston et al. (13) reviewed the scientific literature with the aim of evaluating the efficacy of 40% dextrose in gel in preventing hypoglycaemia and in reducing the long-term damage associated with neurodevelopment. Two trials including 312 infants were included. It was found that the administration of the gel reduced the mother-child separation (RR= 0.54, 95% CI = 0.31-0.93) and the probability of exclusive breastfeeding after discharge was increased (RR 1.10, 95% CI from 1.01 to 1.18).

	No side effects related to gel administration were detected by investigators, and the group of gel-treated infants showed an increase in blood glucose of 7.2 mg/dl compared to the placebo group. Hegarty et al (7) conducted a clinical trial in which 416 newborns were randomized and assigned to one of 4 types of treatment: dextrose 40% in gel in a single-dose (200 mg/kg) or double-dose (400 mg/kg) 1 hour after birth or followed by 3 additional doses of dextrose (200 mg/kg) in the first 12 hours. Blood glucose was measured at 2 hours from birth then every 2-4 hours for the first 12 hours of life. The incidence of hypoglycaemia was lower in the treated than in the control group treated with a placebo solution (41% vs 52%, RR = 0.79 (0.64-0.98), p = 0.03). The group of newborns treated with a single administration of gel at a concentration of 200 mg/kg showed a greater reduction in the incidence of hypoglycaemia compared to the other types of treatment (38% vs 56%, RR = 0.66 (0.47-0.99), p=0.04). Treatment with 40% dextrose in gel also led to a reduction in admissions to NICU due to hypoglycaemia compared to the control group (2% vs 13%, RR = 0.12 (0.02-0.90), p = 0.04) and to the number of newborns treated with milk in formula (Mean Difference = -6.00 (-11.58-0.41), p=0.036). Scientific Safety Evidence: No side effects related to the use of 40% dextrose in gel were recorded in all the studies performed. In 2015, the guidelines published by the University of Auckland, New Zealand, stated that the use of dextrose in gel does not change the incidence of neurosensitive disability at 2 years of correct age, moreover, events like crisis convulsive or dead have not been described after the administration of this gel (15). Moreover, from the analysis of the literature by various scientific search engines including Pubmed, Scholar and others, using as keywords: newborn, hypoglycaemia and dextrose gel, until the moment of writing this synopsis, no work has been detected as far as regards the side effects in the use of dextrose gel.
Justification of the non-commercial nature of the study	The present study involves the administration of a nutriment supplement based on dextrose. It falls within the typology of a spontaneous/non-commercial pilot study. It arises from the need of the health care providers to identify a product that can decrease the severity of the incidence of hypoglycaemia related to the perinatal period, limiting the suffering for newborns and families and at the same time reducing the costs charged to SSN deriving from standard pharmacological and rehabilitative therapies in the short and medium-long term. The Destrogel 40% product was chosen because ORSANA ITALIA Srl proved to be available for the supply of the same, also signing a declaration that the scientific results of the research will remain available to the scientific community and that the management of the protection activities intellectual property on any inventions deriving from the research will take place according to the provisions of current legislation and in particular of art. 65 of Legislative Decree 10 February 2005, n. 30 “Industrial Property Code. Therefore, the results of the research will remain available to the Scientific Community and will not be used for profit or commercial purposes.

Registration status and marketing of the product in the studio	Health Ministry registry non-drug products. **The product is present in the food register for special medical purposes of the FARMADATI Italia website (https://www.farmadati.it/) and classified with the following code: 974921607. The product has been notified for marketing in Italy pursuant to DPR 57/2002 and intended for the dietetic treatment of hypoglycemia.** Ingredients: Water, Dextrose, Food Pectin Description: Destrogel 40% is food for special medical purposes. It looks like a clear gel, slightly yellow, with a sweet taste. Field of use: **Destrogel 40%** is indicated in the case of increased need or reduced intake with the diet of its components in all the different age groups. **Destrogel 40%** may be useful, in particular, in the prevention of hypoglycemia in newborns who have 1 or more risk factors.
Objectives of the study	• **Primary objective:** To assess whether a single administration of Destrogel 40% micronutrient can reduce the incidence of hypoglycaemia in late term newborns and in SGA and LGA term infants (gestational age: 37-42 weeks). • **Secondary objective:** To evaluate whether the administration of the 40% micronutrient Destrogel is able to decrease the incidence of the use of formula milk and the intravenous administration of 10% glucose solution in late term infants and in SGA and LGA term newborns (gestational age: 37-42 weeks), reducing artificial breastfeeding in favour of breastfeeding and also reducing the pain of the newborn during the execution of peripheral venous access for the administration of hypoglycaemia therapy.
Study design	Pilot study, non-commercial, with a product for special medical purposes, controlled (vs. standard therapy), randomized with a 1: 1 ratio, open.
Study population and number	Late preterm, full-term newborns, SGA and LGA (<10th and> 90th centiles of body weight). 1. **Inclusion Criteria** **Mothers:** -Favourable for breastfeeding -BMI between 19-24 **Newborns:** -Late preterm (gestational age: 34-36 weeks) -Term neonates (gestational age: 37-42 weeks), with body weight <10th

	centile (SGA) or> 90 ° centile according to Bertino's neonatal anthropometric evaluation -Born from eutocic childbirth -Rooming-in -Body temperature between 36.5-37.5 ° C 2. **2. Exclusion criteria** **Mothers:** -Lack of informed consent -Diabetic mother -Taking medicines during pregnancy (beta blockers, tolbutamide) **Newborns**: - Major congenital malformations - Blood sugar <47 mg / dl - Body temperature <36.5 ° C or> 37.5 ° C - NICU admissions - Milk intake in formula - Intravenous infusion of 10% glucose solution - Metabolic and respiratory acidosis (pH: 7.28 - 7.38) **Number of patients to be enrolled** Enrolment of a total of 172 newborns is planned, divided into 4 groups: **Group A:** 43 newborns at risk of hypoglycaemia to which a placebo solution will be administered (0.5 ml / kg) **Group B**: 43 newborns at risk of hypoglycaemia to which a placebo solution will be administered (1 ml / kg) **Group C:** 43 newborns at risk of hypoglycaemia to which a solution of dextrose 40% in gel will be administered (0.5 ml / Kg) **Group D:** 43 newborns at risk of hypoglycaemia to which a solution of dextrose 40% in gel will be administered (1 ml / Kg).
Randomization	After enrolment, patients will be randomly divided into groups A, B, C, D, using statistical software.
Number of centres	Monocentric pilot experimentation. The center will be the Poliambulanza Foundation Hospital Institute, Department of Mother and Child Health.
Sample Size	The sample size will be calculated through G * Power 3.1.9.2 for Windows. The incidence of neonatal hypoglycaemia in the neonatal population is 30% and of these 50% develop hypoglycaemia. Hegarty et al (7) tried to show that the use of 40%

	dextrose in gel could reduce the rate of hypoglycaemia to 25%, but only achieving a reduction to 41%. We believe that in this study the children of a diabetic mother were a considerable confounding factor and could mask the beneficial effects of dextrose on the sample of late preterm and SGA-born and LGA-born infants. To demonstrate this, we have excluded the children of a diabetic mother from the analysis to reduce the rate of hypoglycaemia from 50% to 25% by administering 40% dextrose in gel. Placing α = 0.05, β = 0.1, Power = 0.90, Odds Ratio = 0.334, R2 = 0.25, allocation rate = 1: 1, distribution X = binomial, the number of samples required is 172. In each group therefore will be allocated 43 babies. This is the minimum number that can be recruited. We will take into consideration any disclaimers during the study (parents can ask not to continue the treatment at any time) which goes beyond the statistical calculations. Therefore, if necessary, we will recruit a sufficient number of infants to reach the minimum number that can be recruited according to the protocol design.
Treatment and Posology	***Administered products:*** **Dextrose group:** Destrogel 40% ***Active ingredient: Dextrose*** Excipients: Water, Food Pectin. Placebo Group: Composition: Water, Food Pectin. ***Placebo Group:*** • **Group A:** newborns at risk of hypoglycaemia who will be given a placebo gel solution (0.5 ml/kg equivalent) • **Group B:** newborns at risk of hypoglycaemia who will be given a placebo gel solution (1 ml/kg equivalent) Dextrose Group: • **Group C:** newborns at risk of hypoglycaemia to which a solution of dextrose 40% in gel will be administered (0.5 ml/kg equivalent to 200 mg/kg) • **Group D:** newborns at risk of hypoglycaemia to which a solution of dextrose 40% in gel will be administered (1 ml/Kg equivalent to 400 mg/Kg).
Route of administration	In the categories at risk of hypoglycaemia the gel will be administered by massaging it into the buccal mucosa.
Duration of the administration period	The administration will be carried out 1 hour after birth.
Duration of the study	***Duration of the observation period of the enrolled patient*** From birth up to 48 hours of life ***Total duration of the study:***

	The study will last one year: the first 11 months will be assigned to enrol clients in the centres concerned. In this period the planned laboratory investigations will also be present. The last month will be used for the study and analysis of the results obtained.
Procedure	**Method:** At birth, newborns who fall within the inclusion parameters will be randomly recruited and divided into 4 groups (A, B, C, D). The medical staff will be informed of the progress of the study. Eligible parents will be informed about the nature and purpose of the study in order to obtain informed consent to participate in the study. In the categories at risk of hypoglycaemia, the administration of the gel, which will be massaged into the buccal mucosa, will be performed 1 hour after birth. Glycaemic monitoring will be carried out at 2, 4, 6, 12 and 48 hours of life as required by the department protocol. The detection of blood glucose and blood gas values will be carried out through a capillary heel extraction already foreseen by the department procedures. The sample will be analysed with "ABL90 Flex". Each detection will be preceded by the measurement of body temperature via the skin (Covidien Filacada). Newborns will be exclusively breastfed after the administration of the gel and during the first 48 hours of life. All data will be collected by the data collection form. The newborns who present blood glucose values <47 mg/dl will be treated with formula milk (formula 1 milk) or 5% intravenous infusion of glucose according to the protocol of the department. **Evaluation parameters:** **Effectiveness** Reduction of the incidence of hypoglycaemia in neonates at risk **Tolerability** Any side effects that may be observed by the doctor will be recorded on the data collection form.
Basal Visit	At birth, as required by neonatal protocols, newborns will undergo medical examinations.
Control Visit	From the delivery room the babies will be transferred to the nursery where they will be subjected daily to several check-up.
Follow-up	As required by the neonatological protocols.

Statistical Analysis	Statistical analysis will be performed by IBM SPSS Statistics for Windows, version 20.0 (Armonk, NY: IBM Corp.). The normal distribution of data will be evaluated by Shapiro-Wilk test. The homogeneity of the groups will be analysed by ANOVA test or chi-square test, respectively if the variables are continuous or discrete. If the data do not present a normal distribution, they will be analysed by Kruskal-Wallis test. The multiple logistic regression test (corrected for the risk factors for hypoglycaemia: sex and age) will finally be used to estimate the odds of hypoglycaemia between the placebo or dextrose 40% gel groups. Secondary outcomes will also be studied with the multiple logistic regression test.

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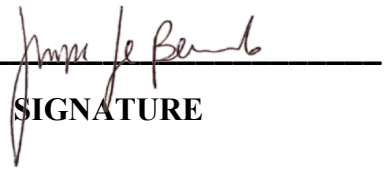	3-12-2019
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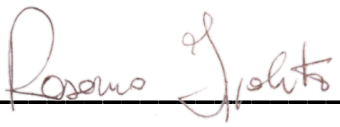	3-12-2019
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