Consensus Clinical Guidelines for Screening & Management of Hypoglycemia in Late Preterm and Term Infants (≥ 34 weeks GA)
UCSF NCNC (Northern California Neonatology Consortium)

PART I: Background

- **Risk factors for neonatal hypoglycemia**
  - Inadequate glycogen stores
    - Small for gestational age (SGA)
    - Intrauterine growth restriction (IUGR)
    - Prematurity (<37 weeks gestational age)
    - Post-term gestation (≥42 weeks gestational age)
  - Increased glucose utilization
    - Large for gestational age (LGA)
    - Infant of a diabetic mother (IDM)
      - Includes mothers with pre-existing diabetes (DM1 or 2) or gestational diabetes (GDMA1 = diet-controlled or GDMA2 = medication-controlled)
    - Conditions which increase metabolic demand: sepsis, encephalopathy, HIE, perinatal stroke, seizures, hypothermia, prematurity, polycythemia, hemolytic disease, metabolic disease, respiratory distress, endocrine abnormalities, congenital heart disease, maternal substance use
  - Hyperinsulinemia
    - LGA
    - IUGR
    - IDM
    - Certain genetic/metabolic conditions (e.g. Beckwith-Weidemann Syndrome)
- **Sequelae of neonatal hypoglycemia**
  - Neurodevelopmental Sequelae
    - Association with worse cognitive and motor performance on developmental testing at 18 months, 3 years, 5 years; lower school achievement in children at 4th grade
    - *NOTE*: recurrent episodes of hypoglycemia are more predictive of long-term sequelae
    - *CAVEAT*: causality has not been determined for these associations, nor effectiveness / safety of screening and intervention to raise glucose levels

PART II: Definition of hypoglycemia

- Definition of hypoglycemia
  - "Plasma glucose concentration below which normal brain function cannot occur"
  - Published thresholds for diagnosing hypoglycemia:
    - *NOTE:* difficult to define a single blood glucose concentration that warrants intervention in every neonate. Published literature and guidelines primarily rely on normative values since defining hypoglycemia based on presence/absence of sequelae or performing prospective clinical trials is impossible.

        - *NOTE:* units for all glucose values are in mg/dL
        - Alkalay, et al. (2006) - estimate of 5th percentile (breast and formula fed infants):
            - 1-2hrs: **27** mg/dl
            - 3-23hrs: **40** mg/dl
            - 24-47hrs: **41** mg/dl
            - 48-72hrs: **48** mg/dl
        - Cornblath & Ichord (2000) - formula fed infants:
            - All infants: **<20-25** mg/dl
            - First 24hrs:**<30-35** mg/dl (sick **<45-50** mg/dl)
            - >24hrs: **<40-50** mg/dl
        - Canadian Pediatric Society (2004):
            - **<32** mg/dl 2hrs post-feed
            - **<36** mg/dl post-subsequent feed
        - American Academy of Pediatrics (AAP) (2011):
            - Birth-4hrs:**<25** mg/dl (target >40 mg/dl)
            - 4-24hrs: **<35** mg/dl (target >45 mg/dl)
        - Academy of Breastfeeding Medicine (ABM) (2014):
            - **<20-25** mg/dl requires intervention (goal **>40** mg/dl)
- UCSF NCNC consensus thresholds for hypoglycemia:
    - *NOTE:* values based primarily on 2011 AAP Clinical Report
    - Target/goal neonatal glucose:
        - **≥ 45** mg/dl prior to routine feeds @ 0-24 hours after birth
        - **≥ 50** mg/dl prior to routine feeds @ >24 hours after birth

PART III: Screening of asymptomatic, at risk infants

- Screening criteria for <u>asymptomatic, well-appearing, at risk</u> infants
    - IDM (pre-existing maternal diabetes, GDMA1, GDMA2)
    - Growth Restricted or Macrosomic (defined by average of male & female weights on Fenton 2013 intrauterine growth curves):
        - Growth Restricted (<5th%)
        - Macrosomic (>97.5th%)
        - *NOTE:* use of a strict birthweight criteria for all term infants is no longer recommended (e.g. <2500, >4000)

	37-37$^{+6/7}$ weeks	**38-38$^{+6/7}$ weeks**	**39-39$^{+6/7}$ weeks**	**40-40$^{+6/7}$ weeks**	**>41 weeks**
Growth restricted (<5th%)	**2280 g**	**2470 g**	**2650 g**	**2820 g**	**3000 g**
Macrosomic (>97.5th%)	**3950 g**	**4180 g**	**4400 g**	**4630 g**	**4880 g**

    - Late preterm (34-37 weeks)
    - Post term (≥42 weeks)
    - *Additional consideration:* neonates with conditions known to be associated with secondary hypoglycemia (i.e., polycythemia, sepsis) should also be considered for hypoglycemia screening

- Method of screening
    - Glucometer
        - *NOTE:* accuracy in low range can depend on make/model of glucometer.
        - *** Thresholds for repeating low point-of-care-testing (POCT) glucose may differ depending on the device and laboratory; follow your local institutions guidelines for repeating low POCT glucose tests.*
            - Consider repeating for POCT values </= 40
            - NOTE: sample should be drawn from warmed heel stick
        - *NOTE:* Consider initiating treatment for hypoglycemia prior to confirmatory testing if waiting for laboratory result will delay treatment excessively
- Timing of screening
    - General principles:
        - Initial screen after first (breast)feeding (by ~1 hour after birth)
        - More frequent screening in first 2-4 hours of life, then ***pre-prandial*** screening that is roughly linked to feeding schedule
        - Stop screening at 12 hours for macrosomic, IDM infants (very low risk of late hypoglycemia)
        - Continue screening until 24 hours for growth restricted, late preterm infants (greater risk of late hypoglycemia)
        - Consider 36 hour screening for growth restricted, late preterm infants if glucoses consistently <45 mg/dl in first 24 hours after birth
    - Time points for Glucose Screening: ~1, 2, 4, 6, 9, 12, 24 hours unless intervention is required
    - "Early exit": consider discontinuing glucose screening prior to completion of all time points in asymptomatic infants with "stable", "normal" glucoses in the first 24 hours after birth:
        - Glucoses >45 mg/dl on 3 occasions
        - Repeat one pre-prandial glucose measurement at 24 hours after birth for growth restricted, late pre-term infants
        - *NOTE:* these recommendations are consensus-based; no specific evidence is currently available to support these recommendations

PART IV: Management of asymptomatic infants

- See APPENDIX 2 for summary clinical pathway / decision tree (ASYMPTOMATIC)
- Intervention thresholds (see PART II above for details):
    - *NOTE:* treatment thresholds vary at 0-4 hours and 4-24 hours after birth to reflect changing physiology / normal values during transition to postnatal life
- Treatment:
    - See algorithm for full work flow and indications for treatment
    - Oral feeding (breast or formula):
        - Method:
            - Breastfeeding
                - Re-check glucose 1 hour after *initiation* of feeding
                - Repeat breastfeeding if glucose remains below threshold; if glucose remains below threshold after >2 breastfeeding attempts, then consider oral formula supplementation

- Oral administration of expressed maternal breastmilk (MBM) is also an acceptable form of treatment

- Formula
  - Use protein hydrolysate formula (i.e., Alimentum, Nutramigen, Pregestimil) preferentially if available to reduce exposure to cow milk protein
    - 1-4 hours → 10-20 mL
    - 4-24 hours → 15-30 mL
  - Re-check glucose 1 hour after *initiation* of feeding
  - If glucose remains below threshold after >2 oral feedings, then consider IV treatment

- Oral glucose gel
  - Method:
    - Glucose (Dextrose) 40% gel
    - Administer 0.5 ml/kg with max of 2.5 mL
    - Dry newborn's mouth with 2x2 gauze
    - Massage the ordered amount of glucose gel using gloved fingertips into the buccal mucosa, instilling no more than 0.5ml into each cheek at a time
  - Important considerations
    - MAXIMUM of THREE doses per 24 hours of oral glucose gel before proceeding to IV treatment.
    - Consider IV treatment prior to 3rd dose of oral glucose if infant is not having sequentially rising glucoses in response to oral therapy.
- IV treatment:
  - Indications for IV treatments:
    - Glucose levels not responding to oral glucose and feeding therapy
    - Persistent hypoglycemia after 3 doses of oral glucose gel
    - Any glucose <35 mg/dl after 5 HOL
  - Method:
    - D10W 2-3 ml/kg IV bolus, followed by:
    - D10W @ 80 ml/kg/day (3.5 ml/kg/hr or GIR=5.5 mg/kg/min)
      - Note: **Glucose Infusion Rate** (GIR) calculated in *mg/kg/min*
        - $\frac{\textbf{IV Rate}\ (\text{mL/hr}) \times \textbf{Dextrose\%}\ (\text{g/dL})}{\textbf{Wt}\ (\text{kg}) \times \textbf{6}}$
      - Increase D10W in increments of 20 ml/kg/day (0.8 ml/kg/hr or GIR 1.4mg/kg/min) for persistent hypoglycemia
      - Peripheral IV (PIV) may use up to 12.5% dextrose solutions (D12.5W). Increasing IV rate will increase GIR, but if approaching 150 ml/kg/day (6.25 ml/kg/hr) consider using higher dextrose% to avoid fluid overload.
      - For persistent hypoglycemia requiring increasing GIR, consider obtaining central venous access early (e.g., UVC, PICC) to administer high-dextrose fluids (>D12.5).

- Continue IV treatment until glucose levels are stable >50 mg/dl, then wean IV gradually
- If persistently hypoglycemic, consider further evaluation for underlying etiology in parallel with treatment. ***Strongly consider involving neonatology, obtaining central venous access, and consulting endocrinology prior to starting glucagon, octreotide, or other therapies.***

PART V: Management of symptomatic infants

- See APPENDIX 3 for summary clinical pathway / decision tree (SYMPTOMATIC)
- Symptoms of hypoglycemia may include:
  - General symptoms:
    - Abnormal cry, poor feeding, hypothermia, diaphoresis
  - Neurologic symptoms:
    - Tremors, jitteriness, hypotonia, irritability, high-pitched cry, lethargy, seizures
  - Cardiorespiratory disturbances:
    - Cyanosis, pallor, tachypnea, apnea, cardiac arrest
- Differentiation of "concerning" ("definite") versus "possible" symptoms of hypoglycemia:
  - "CONCERNING": seizure, lethargy/poorly responsive, hypotonia, apnea, cyanosis
  - "POSSIBLE": jitteriness, tremors, irritability, exaggerated Moro reflex, high-pitched cry, poor feeding, excessive sleepiness/drowsiness
- Thresholds for intervention & treatment:
  - "CONCERNING" (regardless of age)
    - <45 mg/dl → IV treatment
      - Use IV treatment method from PART IV above
    - Recheck glucose **30 min** after intervention
    - If a baby remains hypoglycemic, remember that GIR can be temporarily raised by increasing the IV infusion rate. Watch for signs of fluid overload.
    - Ok to give small aliquots of oral glucose gel (0.5 mL at a time) while obtaining IV access.
    - If symptoms do not resolve after glucose >50 mg/dl, pursue work-up of other potential causes of symptoms. Involve neonatology, obtain central venous access and consider an endocrine consult.
    - **Glucagon:**
      - Option if inadequate glucose response after at least 2 x D10 boluses
      - **If considering Glucagon-** consult Neonatology and administer in consultation with subspecialist
      - If giving IV bolus of glucagon recheck glucose after 30min.
      - Recommended empiric (unambiguously therapeutic) dose:
        - **1.0 mg** glucagon → if AGA infant >/= 3kg
        - **0.5 mg** glucagon → if infant <3kg
      - Clinical response to glucagon suggests adequate glycogen stores in liver and is consistent with a dx of hyperinsulinemia.

- "POSSIBLE" (regardless of age)
  - 35-45 mg/dl→ oral treatment (breastfeeding or formula) + oral glucose gel
  - <35 mg/dl → IV treatment after one attempt at oral feeding
  - Use IV or oral treatment method from PART IV above
  - If symptoms do not resolve after glucose >50, pursue work-up of other potential causes of symptoms

PART VI: NICU and Special Care / Transitional Care Nursery

- Treatment thresholds and treatment methods are different for infants in these higher level care settings; consult neonatology for recommendations

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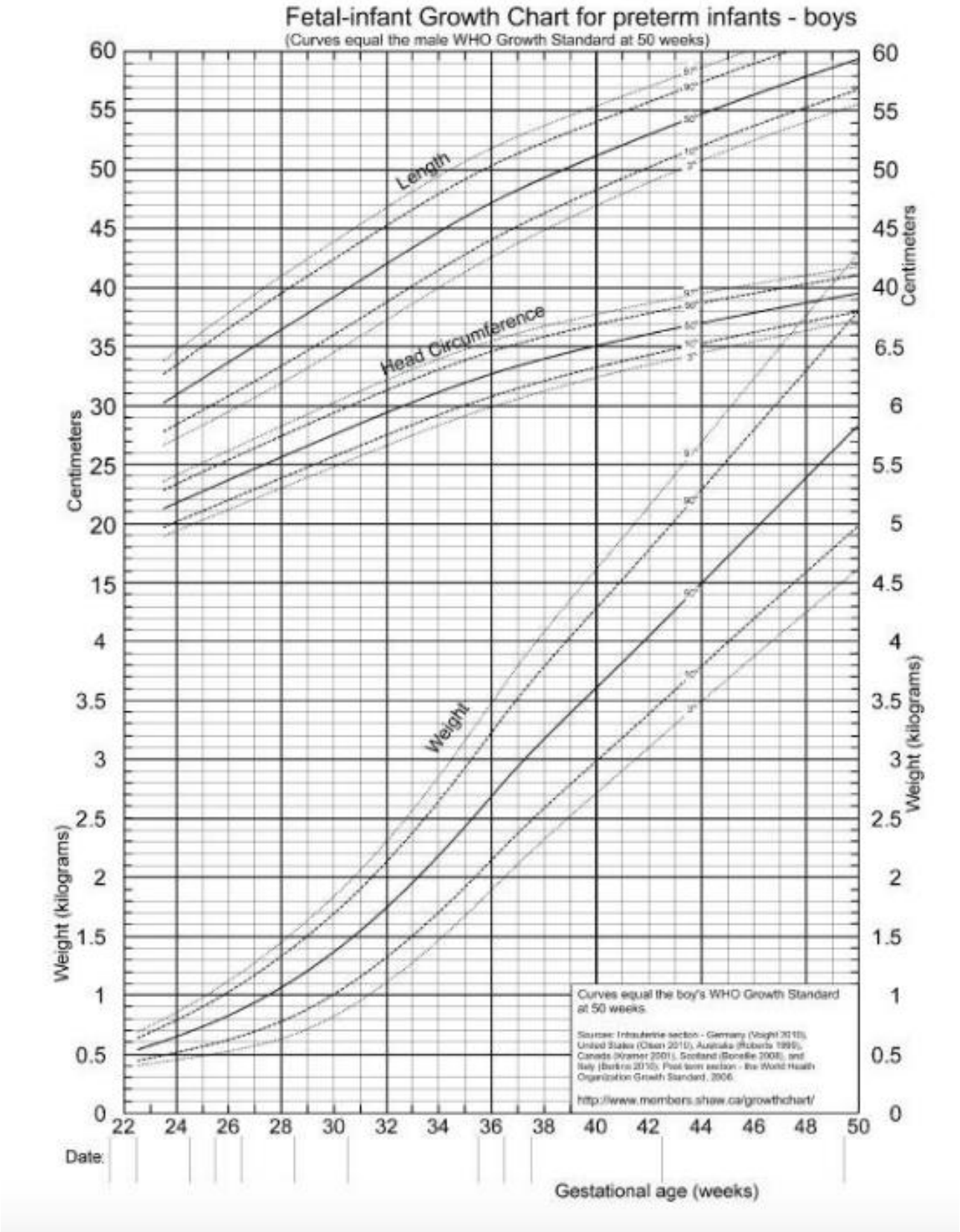
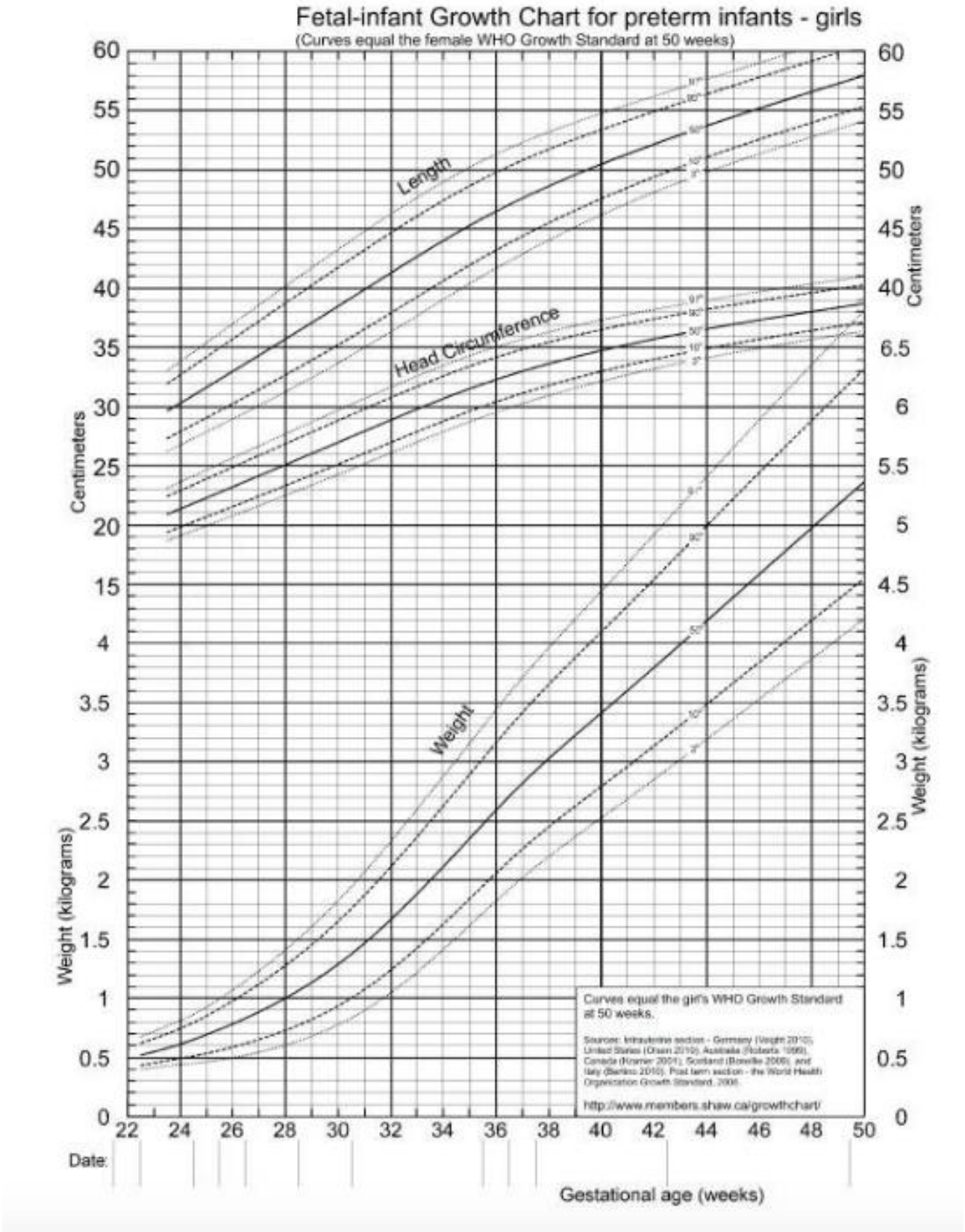
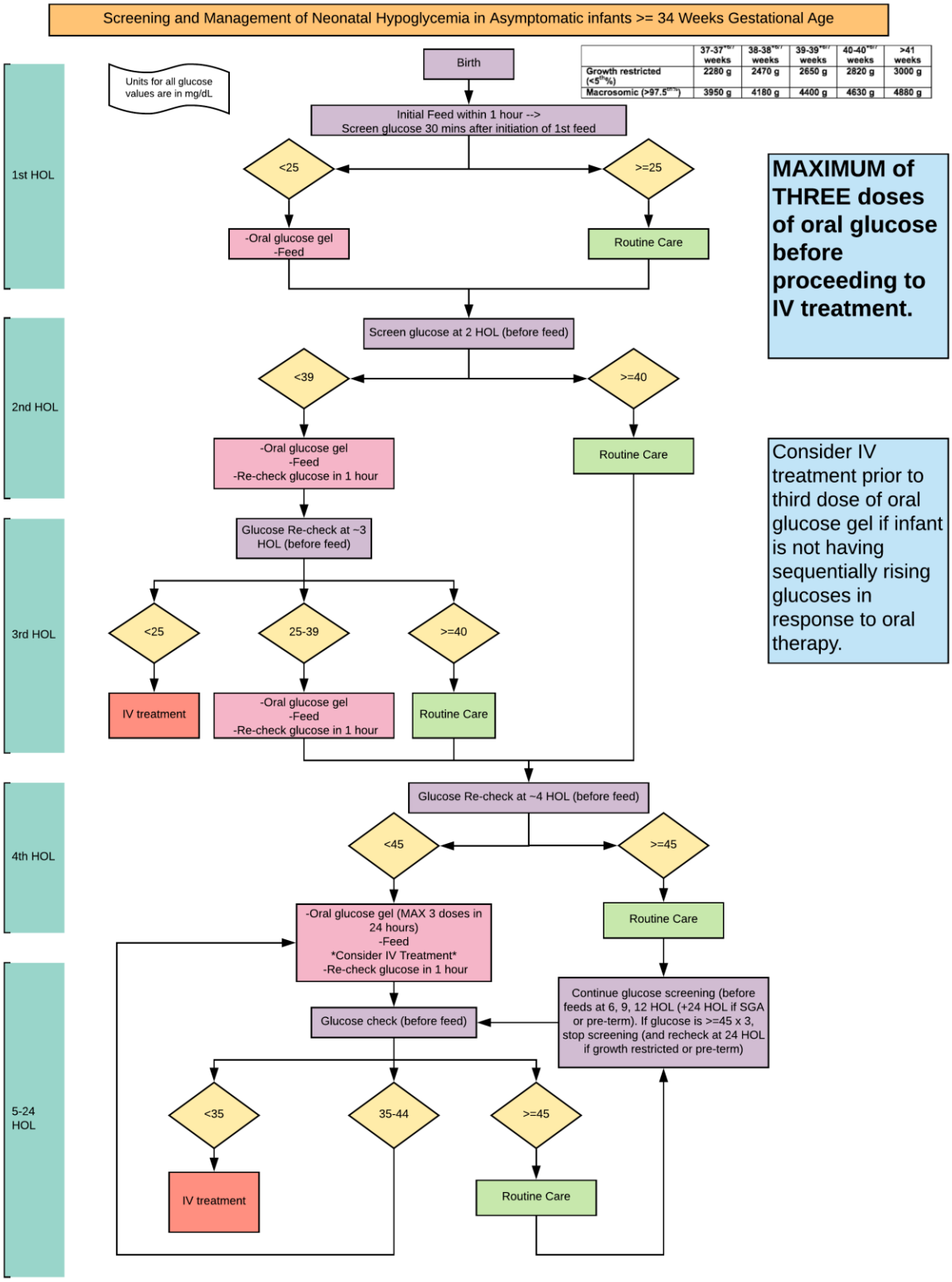
APPENDIX 1: Fenton Neonatal Growth Curves (2013).




Fetal-infant Growth Chart for preterm infants - girls
(Curves equal the female WHO Growth Standard at 50 weeks)
Length
Head Circumference
Weight
Centimeters
Weight (kilograms)
Curves equal the girl's WHO Growth Standard at 50 weeks.
http://www.members.shaw.ca/growthchart/
Date:
Gestational age (weeks)

APPENDIX 2: Screening & Management of Neonatal Hypoglycemia in ***ASYMPTOMATIC*** infants ≥ 34wks GA



APPENDIX 3: Screening & Management of Neonatal Hypoglycemia in ***SYMPTOMATIC*** infants ≥ 34wks GA