Gastrointestinal considerations for extremely preterm infants treated with artificial womb technology

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Objectives

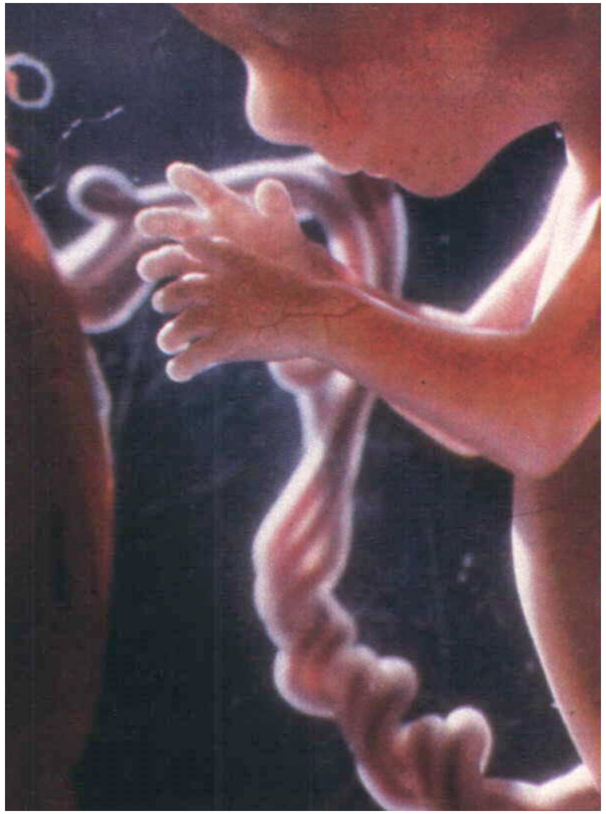
- Review Nutritional Requirements for preterm infants and how to meet them.
- Provide background and historical perspectives of the effects of prolonged parenteral nutrition.
- Provide a perspective on therapeutic strategies.

Fetal Nutrition-Macronutrients

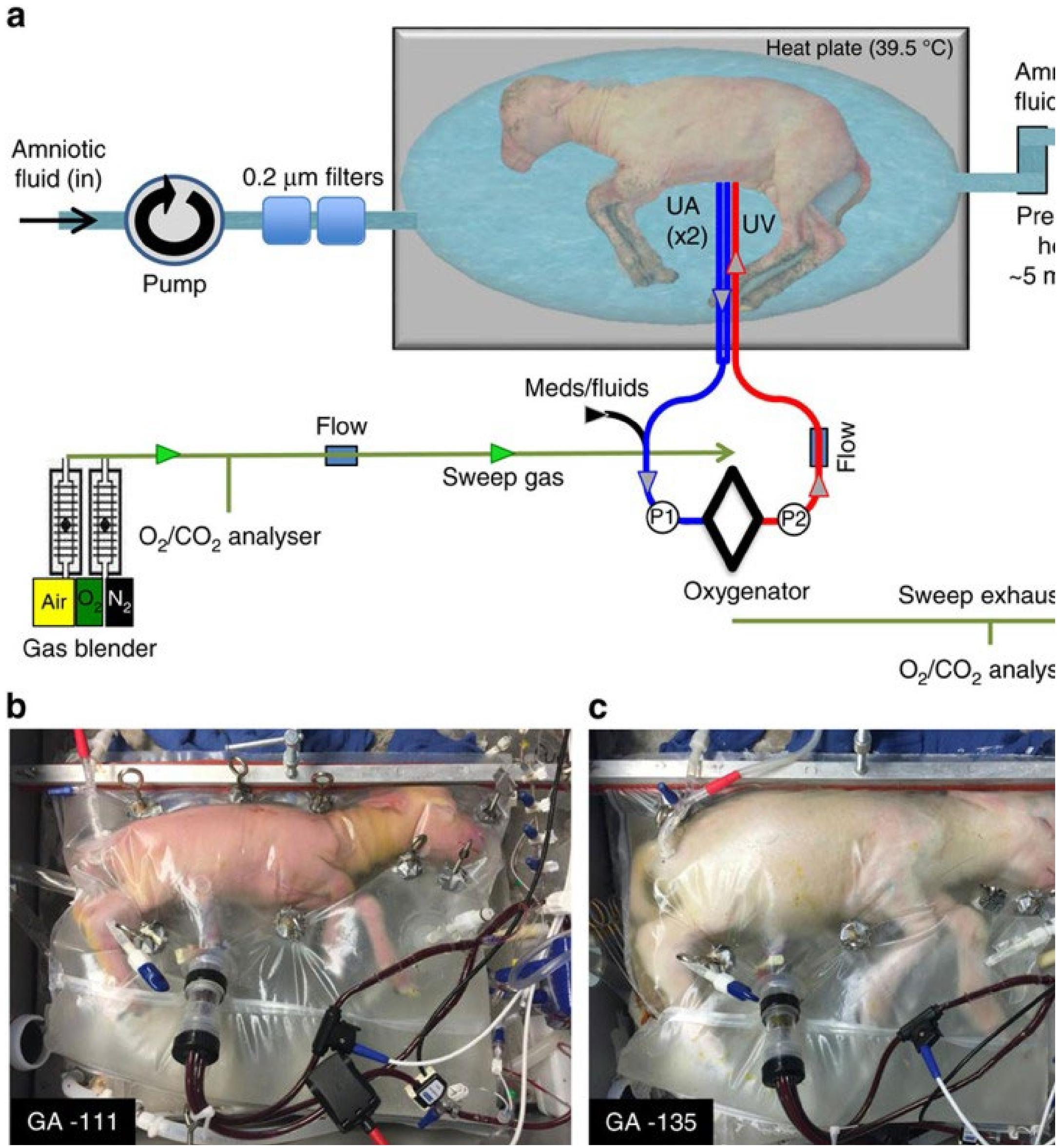
Continuous supply of glucose.

*Protein taken up at about 4 grams/Kg/day.

*Lipids at 3 grams/kg/d .



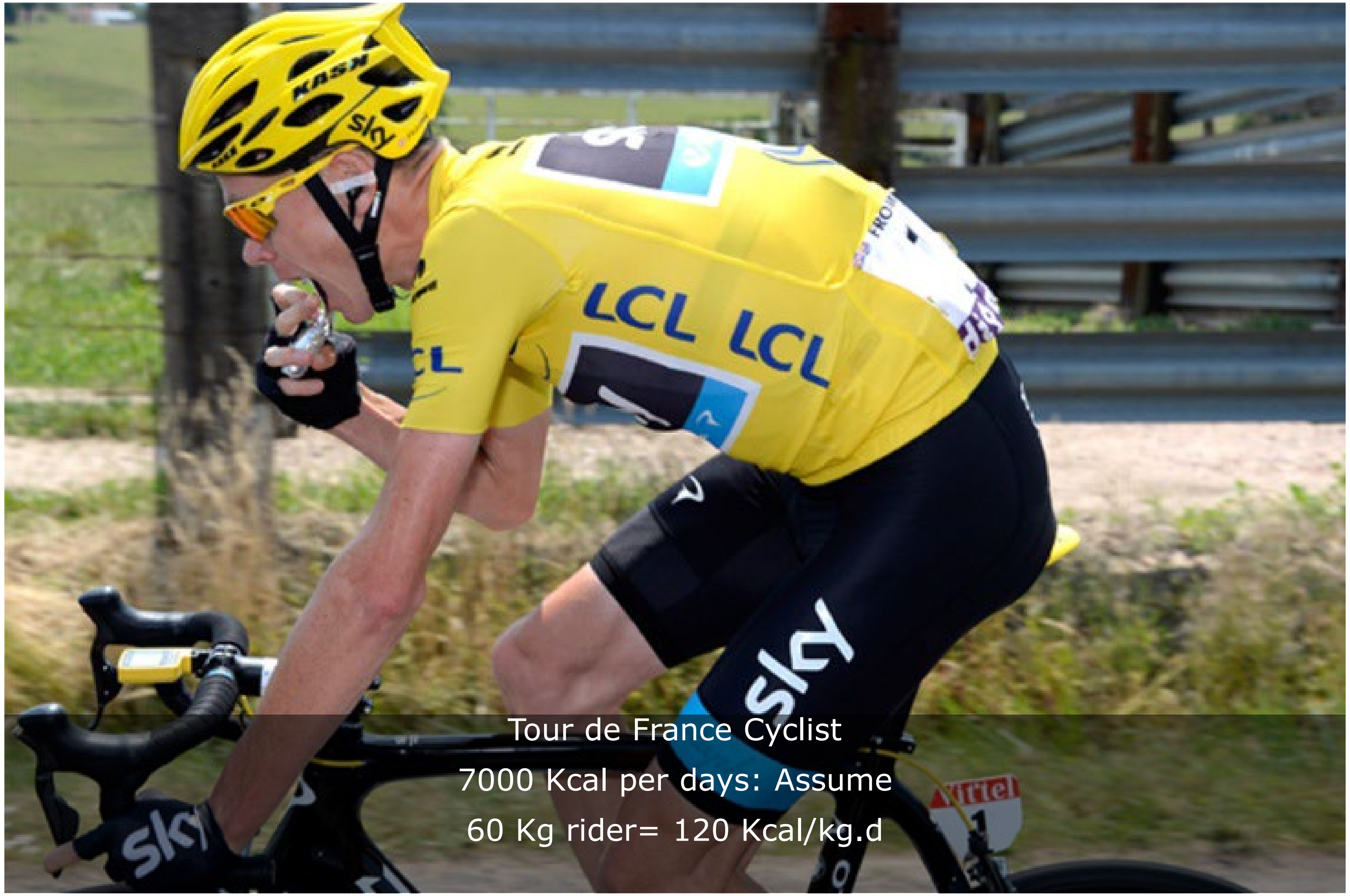
*Ziegler EE, et al Growth 1976:40(4):329-341.


a
Heat plate (39.5 °C)
Amniotic fluid (in)
0.2 µm filters
Pump
UA (x2)
UV
Meds/fluids
Flow
Sweep gas
Flow
O2/CO2 analyser
Air
O2
N2
Gas blender
P1
P2
Oxygenator
Sweep exhaus
O2/CO2 analys
b
c
GA -111
GA -135

Energy Stores in the Fetus and Newborn

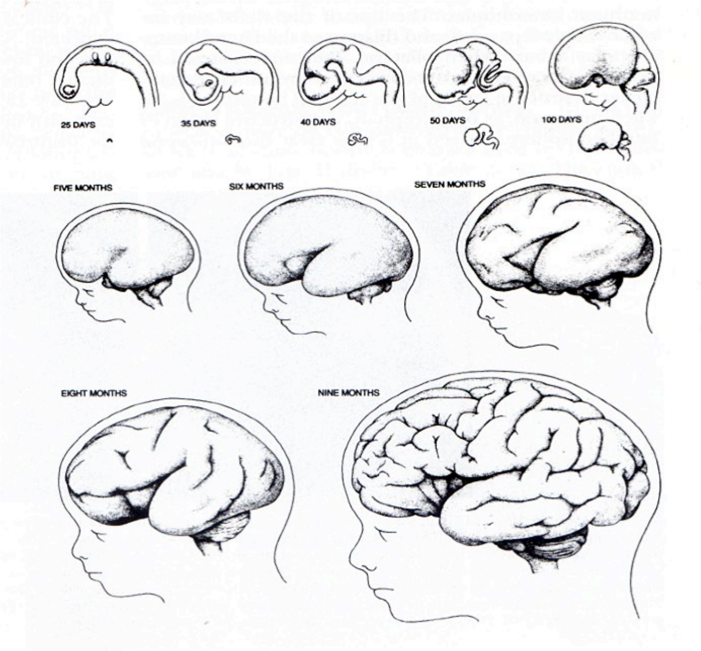
Weeks	Wt (g)	Water (%)	Protein (%)	Lipid (%)	Energy (kcal)
24	690	86.6	8.8	0.1	19.5
26	880	86.8	9.2	1.5	123.6
28	1160	84.6	9.6	5	326.2
40	3450	74.0	12	15.3	3152.4
2 months	5450	71.4	11.4	25	9866

Ziegler, E. Growth, 1976



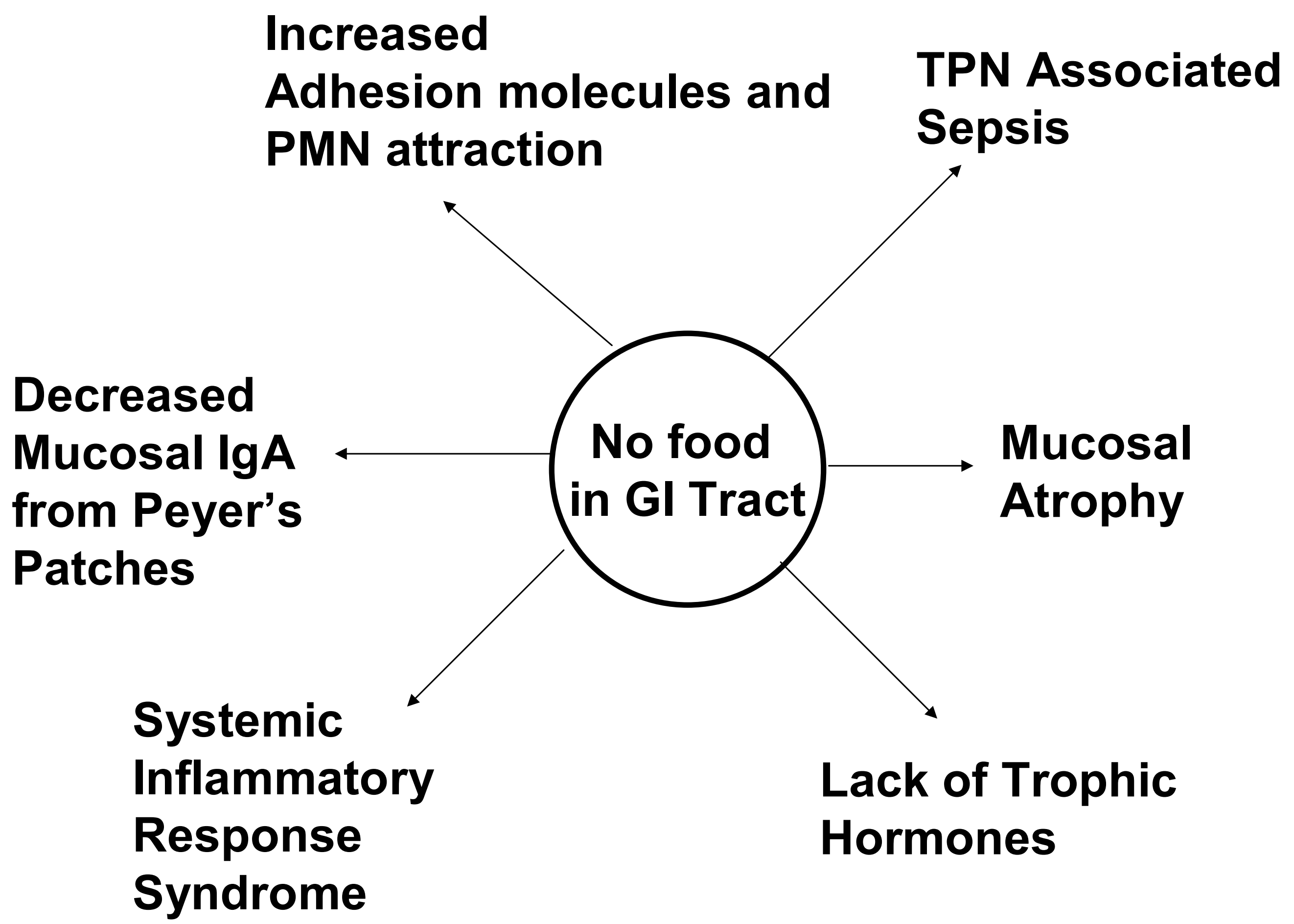
Tour de France Cyclist
7000 Kcal per days: Assume
60 Kg rider= 120 Kcal/kg.d


Requires 120kcal/kg/d

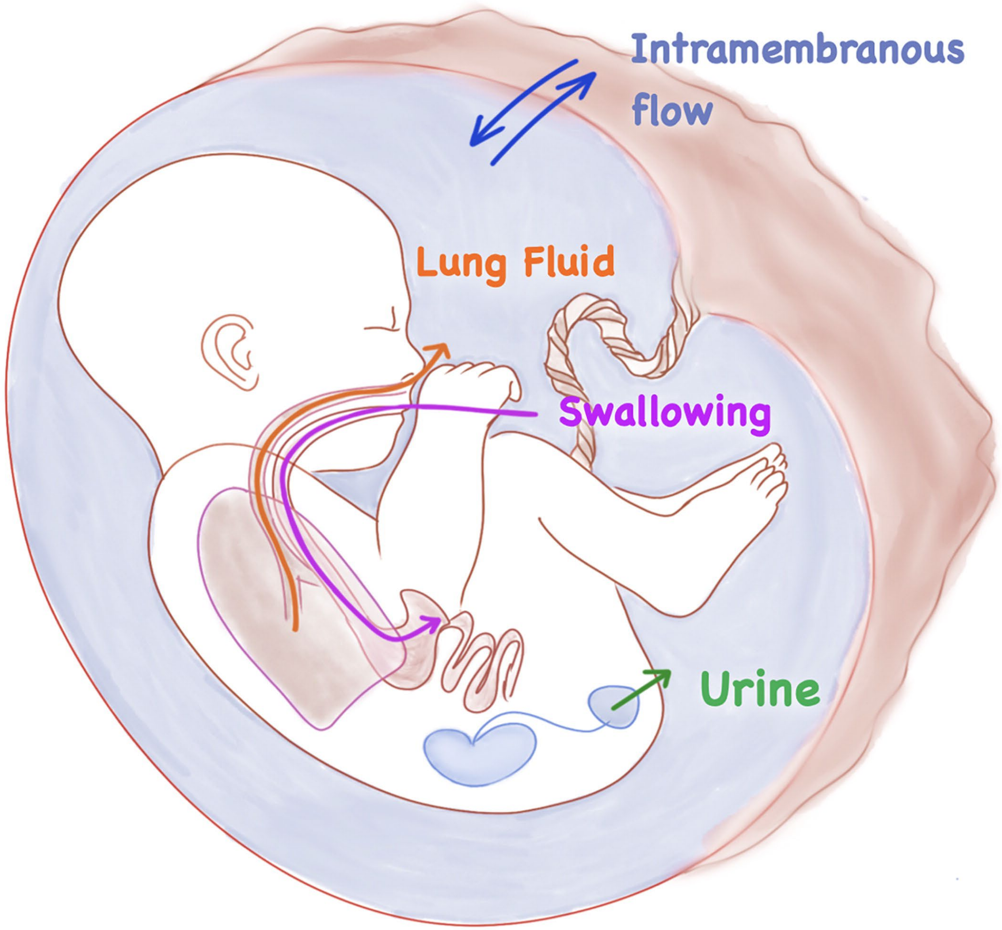


Brain Development through Term Gestation

Consequences of TPN and No Enteral Nutrition

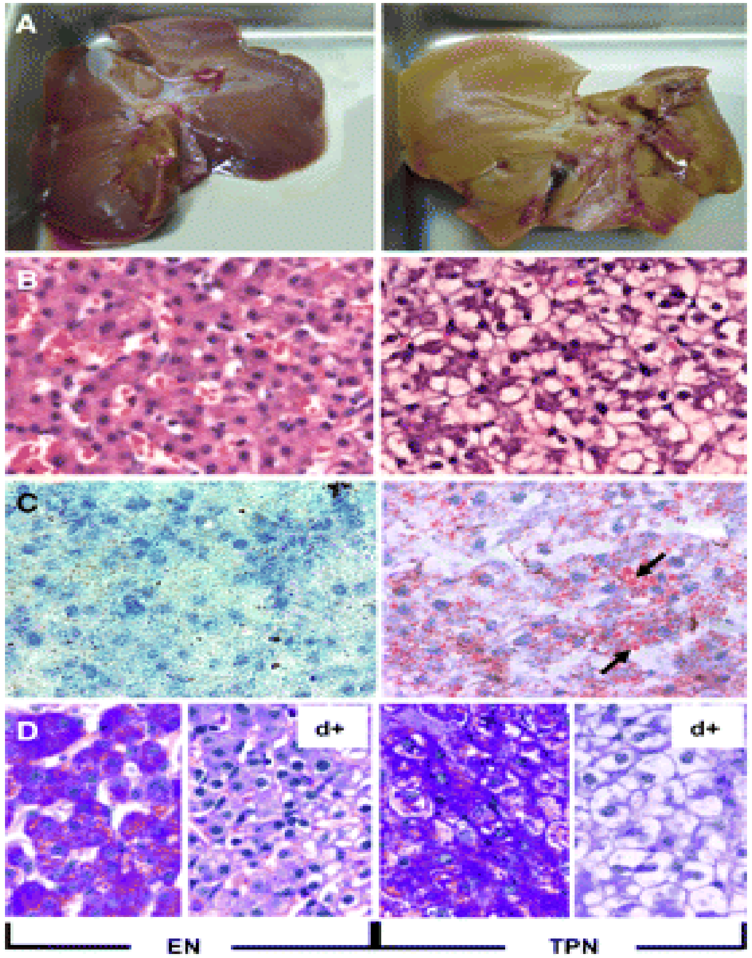


Amniotic Fluid Fluxes



- Swallowing begins at about 13 weeks gestation.
- At term is about 450 ml/day.
- Contains nutrients, trophic factors and immunomodulatory components.

Liver after 7days of TPN vs. Enteral Feeding in Piglets



H & E

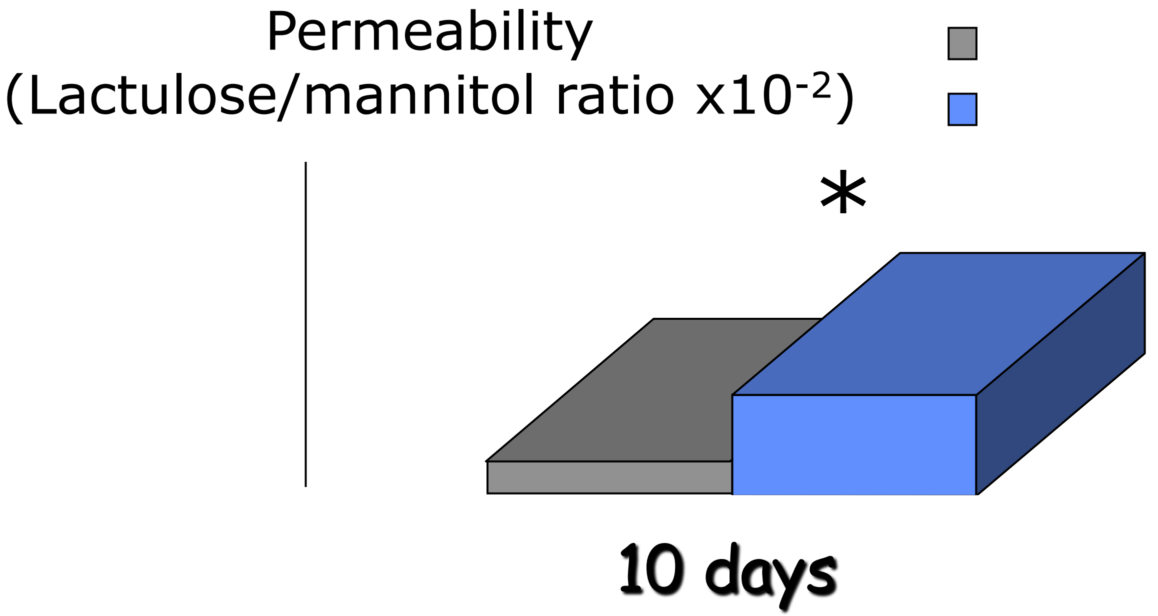
ORO fat Staining

Diastase glycogen staining

Wang, H. et al. J.of Nutrition,2006

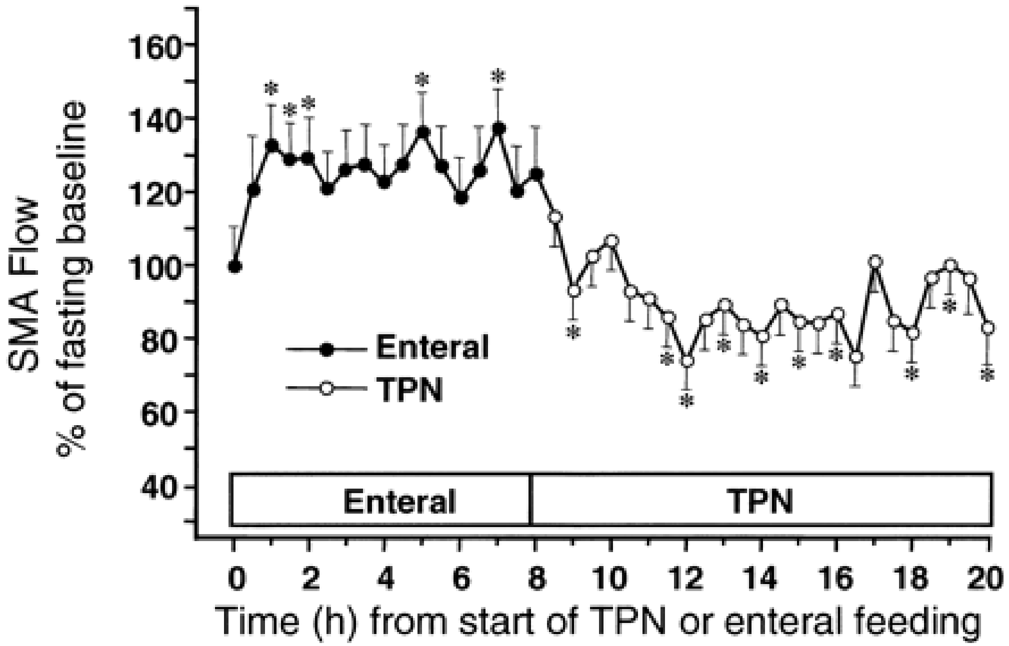
Effect of GI Priming on Intestinal Permeability

Birth weight 1 kg
Gestational age 28 wk



Shulman et al, Pediatr Res 1998;44:519

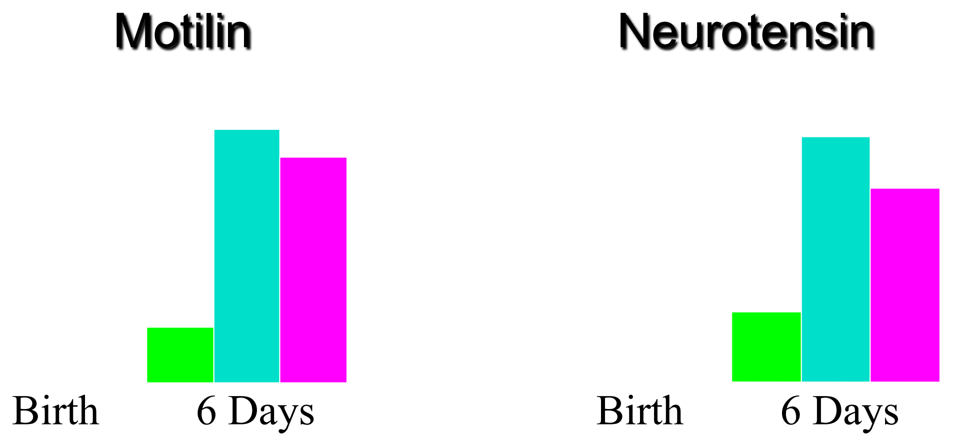
Superior Mesenteric Artery Flow



Niinikoshi, J. Nutrition, 2004

Plasma [GI Hormone] in Premature Infants

- Birth (n=6)
- 6 d, Unfed (n=10)
- 6 d, Fed & well (n=45)
- 6 d, Fed & RDS (n=12)



Lucas, Acta Paediatr Scand 1986; 75:719

The Role of Amniotic Fluid in Fetal Nutrition

By S.J. Mulvihill, M.M. Stone, H.T. Debas, and E.W. Fonkalsrud
Los Angeles, California

● The contribution of amniotic fluid to fetal growth and gastrointestinal tract development was studied in a rabbit model. In the fetal rabbit, at 23 days gestation, 3 conditions were surgically produced: (1) prevention of swallowing of amniotic fluid by esophageal ligation (n = 8); (2) esophageal ligation but insertion of an esophageal cannula distally to allow continuous infusion into the stomach of bovine amniotic fluid to mimic fetal swallowing (n = 7); and (3) sham operation (n = 7). Fetuses were delivered by Caesarean section at 28 days gestation. Esophageal ligation resulted in significant reductions of birth weight and crown-rump length and a trend to decreased liver weight when compared to sham operated controls. Additionally, marked reductions in gastric and intestinal tissue weight and gastric acidity were found following esophageal ligation. These reductions in both somatic and gastrointestinal tract growth and gastric function were reversed by infusion of amniotic fluid intragastrically. We conclude that amniotic fluid provides 10% to 14% of the nutritional requirements of the normal fetus, and that amniotic fluid contains a potent and as yet undefined gastrointestinal tract trophic factor.

INDEX WORDS: Amniotic fluid; fetal nutrition; gastrointestinal development.

It has been suggested that amniotic fluid may be a potential source of human fetal nutrition. It is known that amniotic fluid contains known fetal nutritional substrates including glucose, protein, and lactate.[4] The human fetus swallows up to 750 mL of amniotic fluid each day,[5,6] and fetal intestinal epithelium has the capacity to absorb carbohydrate and protein in the third trimester.[7–9] What is not known is the actual contribution of these mechanisms to fetal nutrition in the face of normal placental function. We have developed a fetal rabbit model to study the role of amniotic fluid in fetal nutrition.

MATERIALS AND METHODS

A total of 31 fetuses from 23 New Zealand doe rabbits were studied. Twenty-two fetuses (71%) survived the operative preparation for study. There were no maternal deaths. All does were time-mated and brought to the laboratory at 19 days gestation for conditioning. At 23 days gestation does were sedated with ketamine (12 mg) and acepromazine (9 mg), half intravenously and half intramuscularly, and then anesthetized with halothane, 1.0% to 2.5% in oxygen administered by mask. A single dose of prophylactic antibiotic was administered preoperatively (penicillin, 200,000 IU

Fetal Esophageal Ligation to prevent swallowing of amniotic fluid

- 32 % reduction in gastric weight
- 40% reduction in serum gastrin
- Gastric acid was 43.7 mumole/ml in controls but 0.5 following ligation
- Infusion of bovine amniotic fluid intragastrially resulted in normal gut development whereas Ringers lactate did not
- Epidermal growth factor in amniotic fluid has a potent effect on both somatic and intestinal growth

Table 4 Roles of various trophic factors found in amniotic fluid in intestinal development and the location of their receptors

Trophic factor	Location of receptors	Role in intestinal growth
EGF	Basolateral intestinal membrane	Stimulates cell mitosis and differentiation Stimulates intestinal epithelial cell proliferation
HGF	Intestinal crypt epithelial cells and in the muscle layers of the intestine	Intestinal cell proliferation *in vitro* and has been demonstrated to induce intestinal growth in rats
TGF-α and TGF-β	Basolateral intestinal membrane	Primary role may be intestinal mucosal repair
IGF-1	Crypt cells, basolateral membrane and in the distal intestine	Primary mediator of both intrauterine and postnatal growth in mammals May be important for growth of muscle growth of distal small intestine
EPO	Apical surface of intestinal epithelial cells	Increased villus height, villus area, crypt depth and crypt epithelia cell proliferation in rat pups. *In vitro*, recombinant EPO has been shown to protect cells against mucosal injury
G-CSF	Apical regions of the intestine	Role in epithelial cell maintenance
IL family	Intestinal epithelial cells	Enhances intestinal epithelial cell restitution. Enhances the integrity of the intestinal epithelial cell junctions. Intestinal epithelial cell proliferation and increased nutrient uptake

IGF-1: Insulin like growth factor-1; EGF: Epidermal growth factor; TGF: Transforming growth factor; HGF: Hepatocyte growth factor; EPO: Erythropoietin; G-CSF: Granulocyte colony stimulating factor; IL: Interleukin.

Calcium and Phosphorus in Human Milk, Term and Preterm Formulas

	Required per Kg/day	Required per 100 kcal	Human Milk per 100kcal	Fortified human milk per 100kcal	Term Formula/ 100kcal	Preterm formula /100kcal	Artificial Womb
Ca, mg	184	170	45	156	75	170	?
P, mg	126	116	21	94	50	85	?

Ziegler, E. Nutritional Care of Preterm Infants, 2014

Take Home Messages

The fetus in an artificial womb environment presents a unique set of challenges.

It may be possible to supply nutrients parenterally, but to provide them in quantities similar to those obtained in utero that provide for optimal growth and development are not known.

The fetus swallows large quantities of amniotic fluid, which provides nutrition (about 15% of requirements), but also bioactive factors such as epidermal growth factor. The trophic effect of these nutrients on the developing intestine in utero have been verified in studies in animal models.