Non-Immunoglobulin Factors in Colostrum: Communication from the Dam to the Calf

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Overview of today's talk

- Introduction
- Effects of colostrum on growth and nutrient use
- Role of colostrum in gastrointestinal tract development
- Colostrum components and the immune system
- Colostrum components and changes in metabolism
- Summary

Goal of The Replacement Program

The primary goal of all heifer programs is to raise the highest quality heifer that can maximize profits when the animal enters the lactating herd.

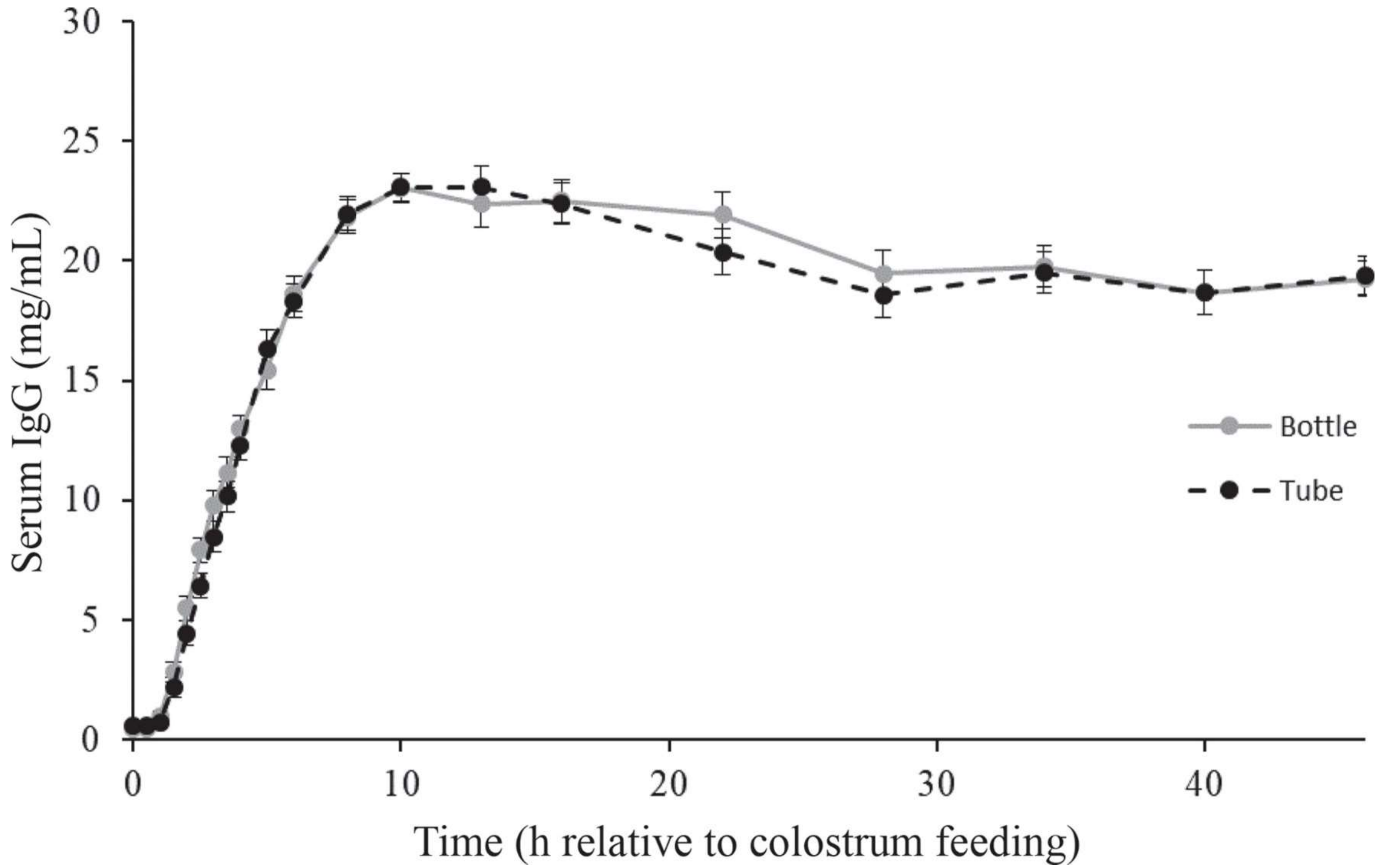
A quality heifer is an animal carrying no limitations – nothing that detracts from her ability to produce milk under the farm’s management system.

Optimize profits by obtaining the highest quality heifer at the lowest possible cost usually in the least amount of time.

Snapshot Evaluation of the Potential Quality of The Replacement

- 1st Calf Heifers "Treated" as Calf/Heifer* ≤30%
  24 hrs. → 3 mos. ____, 4 mos. → fresh ____
- DOAs in first calf heifers ≤7%
  Male DOAs. ____, Female DOAs ____
- 1st Calf avg. peak ≥80% of Mature
  1st Calf lactation total yield ≥80% of Mature
- 1st Calf Culls ≤ 60 Days in Milk ≤5%
- 1st Calf ME's ≥Mature
- 1st Calf "Treated" in Lactation* ≤15%
- 85% retention (any herd) to 2nd lactation ≥85%
- Lower #1 reason for 1st lact. culls(continuous improvement)

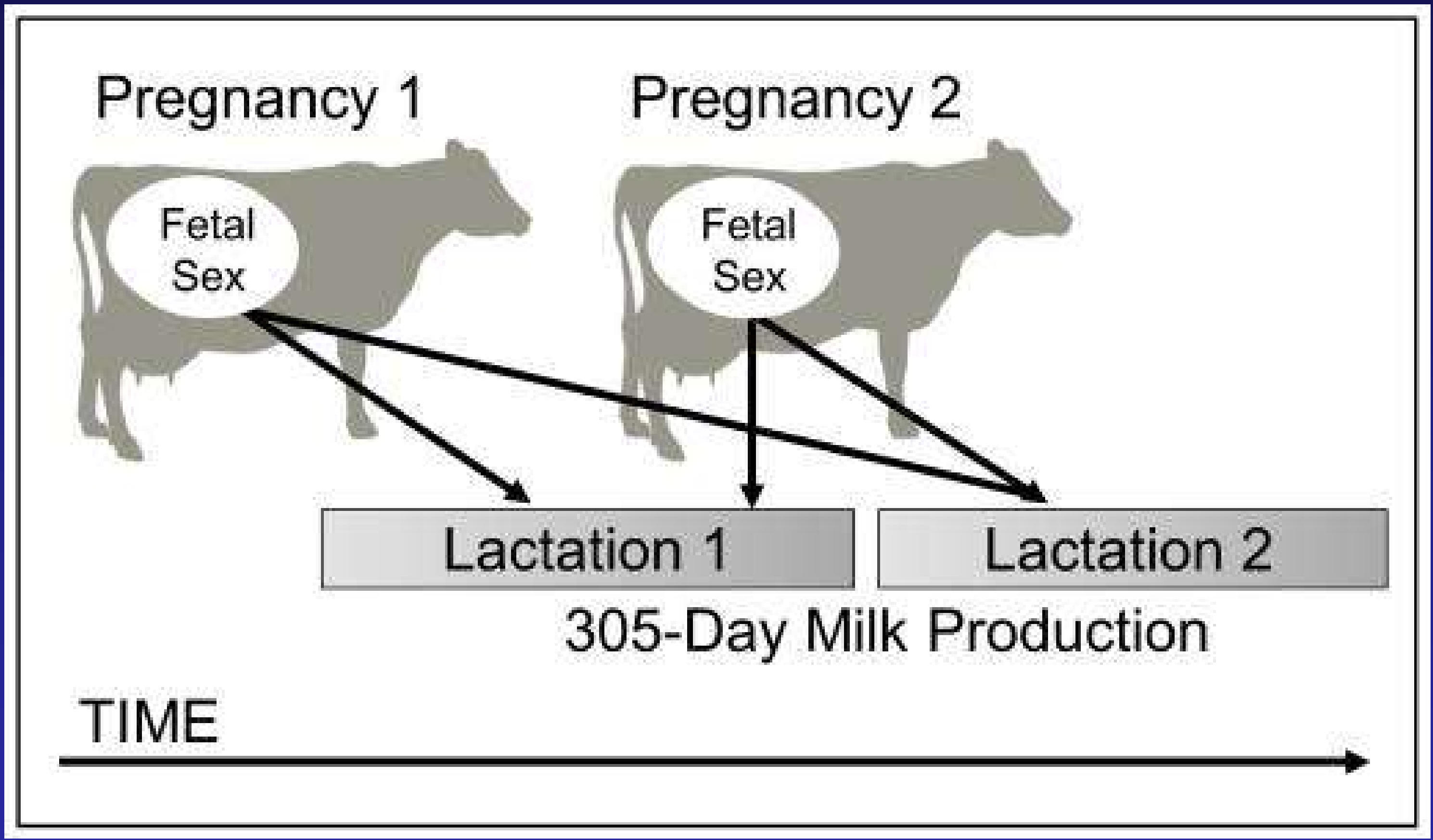
Colostrum by Bottle or Tube Feeder – 3 L



M.Desjardins-Morrissette et al, JDS

So When Does The Process of Creating a Quality Heifer Start?

Holsteins Favor Heifers, Not Bulls: Biased Milk Production Programmed during Pregnancy as a Function of Fetal Sex



Hinde et al. PLosOne 2014 10.1371/journal.pone.0086169

Hinde et al., – Mom's favor heifers

Evaluated the effect of sex of offspring on subsequent milk yield

2.39 million lactations from 1.49 million cattle – U.S. herds

First lactation cattle giving birth to heifers produced 980 lb more milk over the first two lactations

- 490 lb for the first two lactations

Ettema and Ostergaard 2015

- $6 per lactation marginal return for average semen
- $12 per lactation marginal return for sexed semen

Effect of Prepartum Feeding of Ruminally-Protected Choline on Growth of Replacement Heifers (*in utero* effect only)

Age	No Choline	+ Choline	SEM
	n = 17	n = 18	--
Birth, lb	89	84*	2
2 months (weaning), lb	169	171	4
12 months, lb	710	738**	11
Post-calving, lb	1177	1256**	35

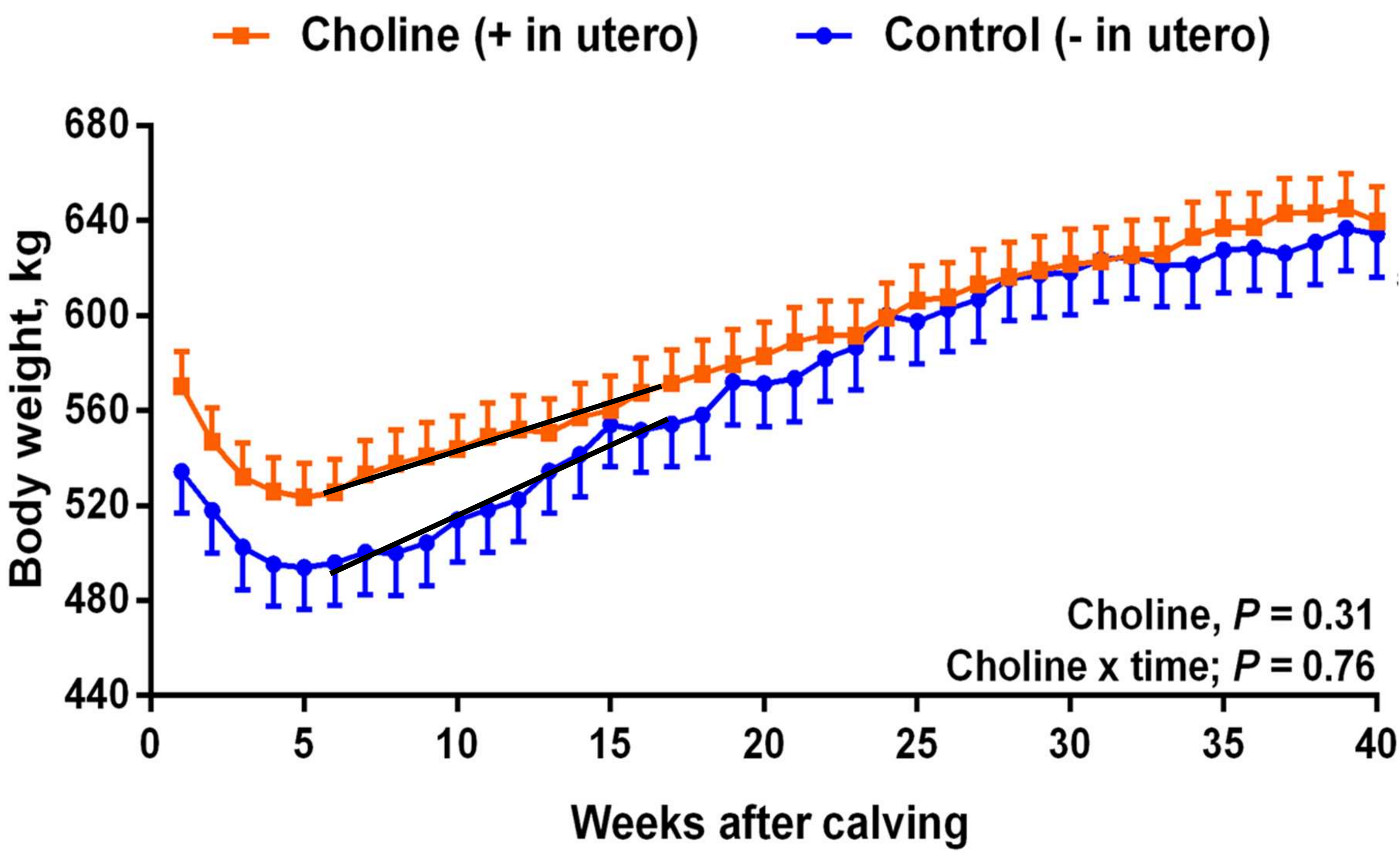
*Effect of choline, $P < 0.10$.

**Effect of choline, $P \leq 0.05$.

Average daily gain from birth to yearlings:
No choline: 1.77 lb per day
Choline: 1.86 lb per day*

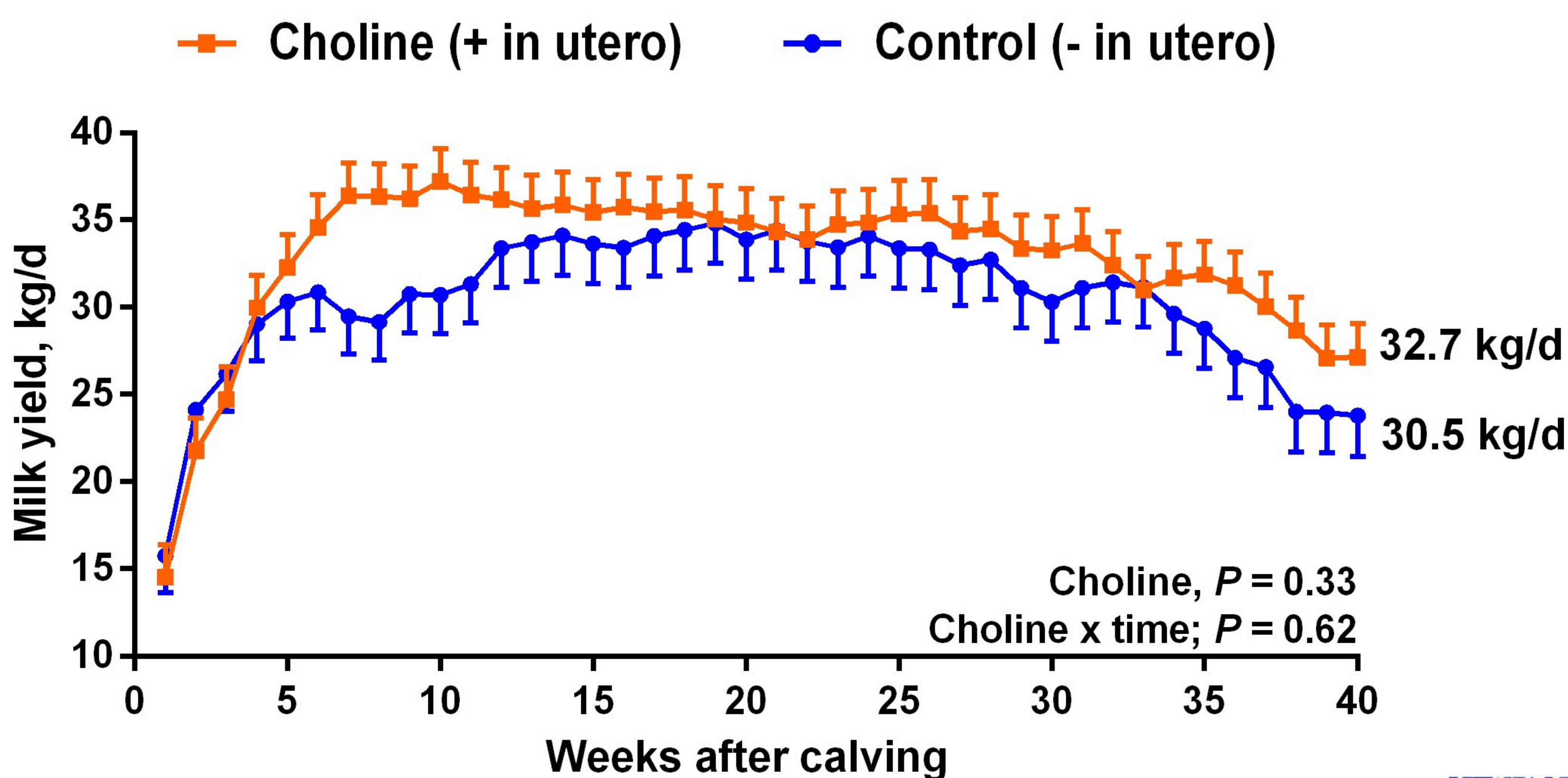
Zenobi et al., 2018. J. Dairy Sci. 101:1088.

Body Weight of Primiparous Cows Exposed to Choline Prenatally



Zenobi et al., University of Florida, 2018.
Unpublished results

Milk Yield of Primiparous Cows Exposed to RP-Choline Biomolecules *in Utero*



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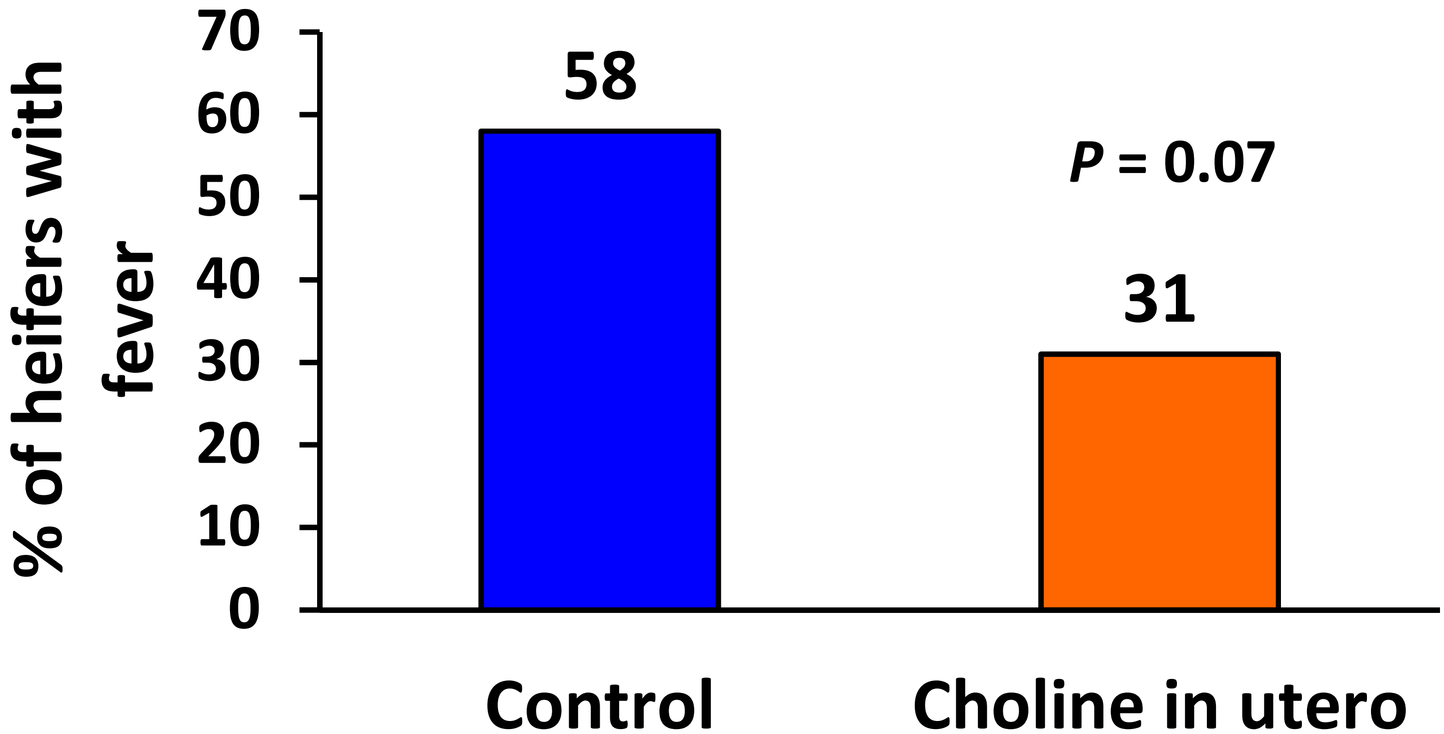
Zenobi et al., University of Florida, 2018.
Unpublished results

In Utero Effects - Incidence of Fever



Rectal temperatures measured daily.
Fever: >103.1°F.

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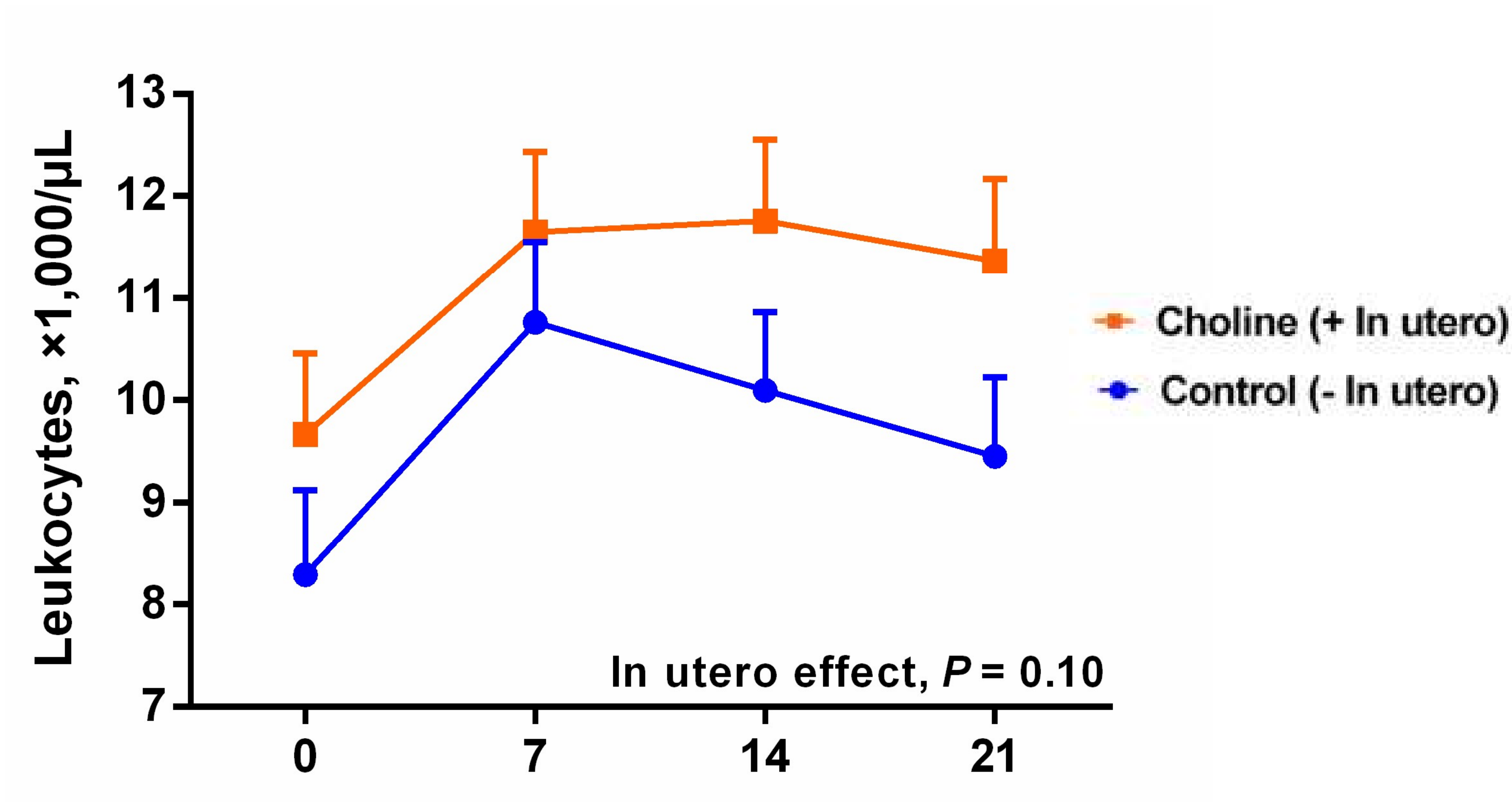
Zenobi et al., University of Florida, 2018.
Unpublished results

Heifers Born from RP-Choline Supplemented Dams Had Increased Concentrations of White Blood Cells



Zenobi et al., University of Florida, 2018.
Unpublished results

Effect of Transition Feeding of RP-Choline on Growth of Replacement Heifers (*in utero* effect only)

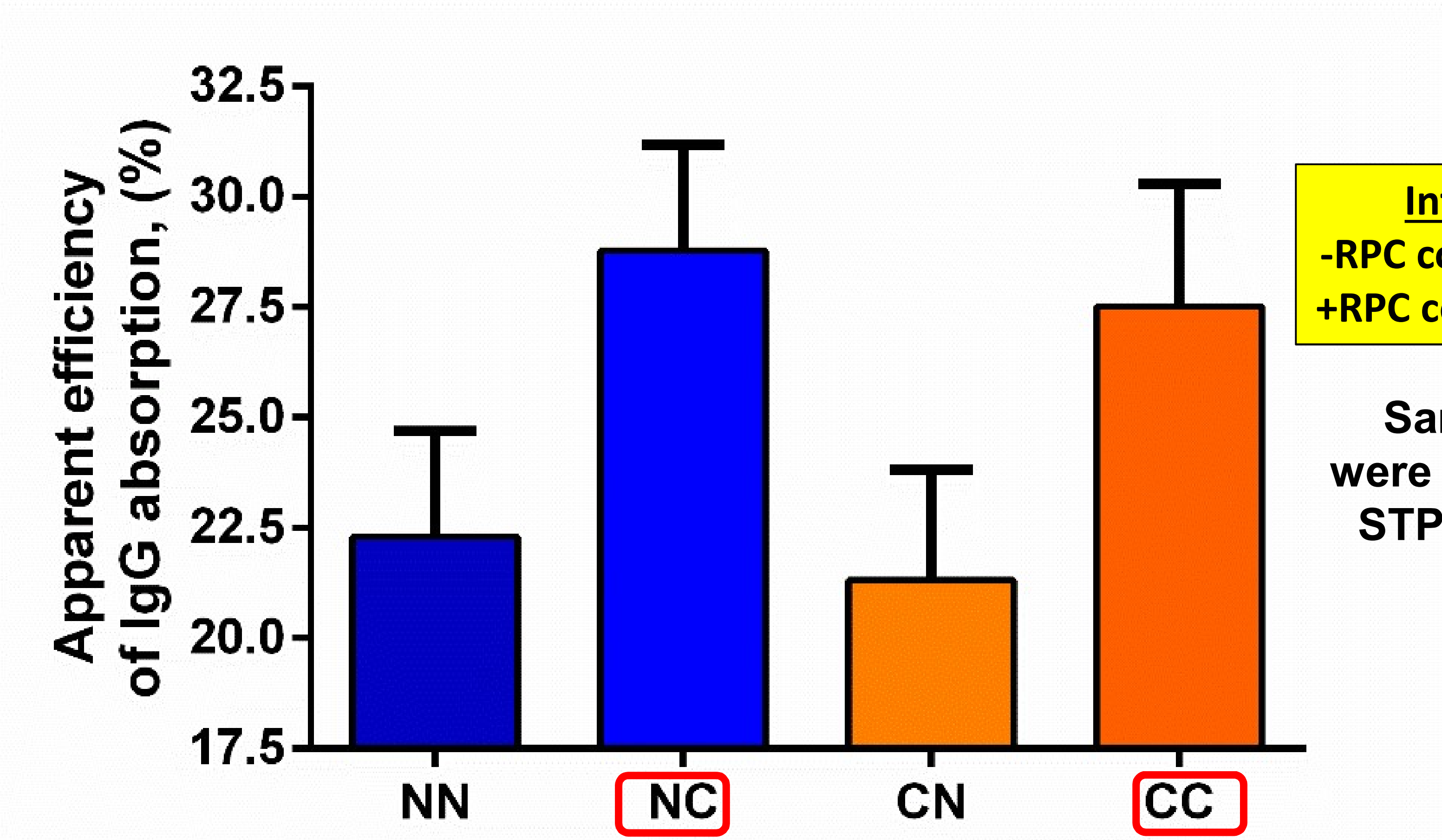
Age	No Choline	+ Choline	SEM
	n = 23	n = 23	--
Birth, lb	92	89	3
56 d of age, lb	161	162	4
300 d of age, lb	604	630	12

*Effect of choline, $P < 0.10$.

Average daily gain from weaning to yearlings:
No choline: 1.70 lb per day
Choline: 1.80 lb per day *

Zenobi et al., University of Florida, 2018.
Unpublished results

Heifers Fed Colostrum Harvested From Dams Supplemented With RP-Choline Had Better Apparent Efficiency of IgG Absorption (n = 59)



Intake of IgG
-RPC colostrum: 382 g
+RPC colostrum: 386 g

Same results were observed for STP and Serum IgG

***In utero*, *P* = 0.66**
Colostrum, *P* = 0.01
Interaction, *P* = 0.96

Summary of *In Utero* Effects or/and Colostrum of RP-Choline on Heifer Calf Responses

- Greater concentration of white cells.
- Less incidence of fever (31% vs. 58%).
- Greater intake of milk replacer and starter the first 21 d
- Greater ADG the first 300 days of life.

- Greater IgG absorption and serum total protein if heifers were fed colostrum harvested form choline-fed dams.

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The lactation cycle and the opportunity to provide bioactive factors to the offspring

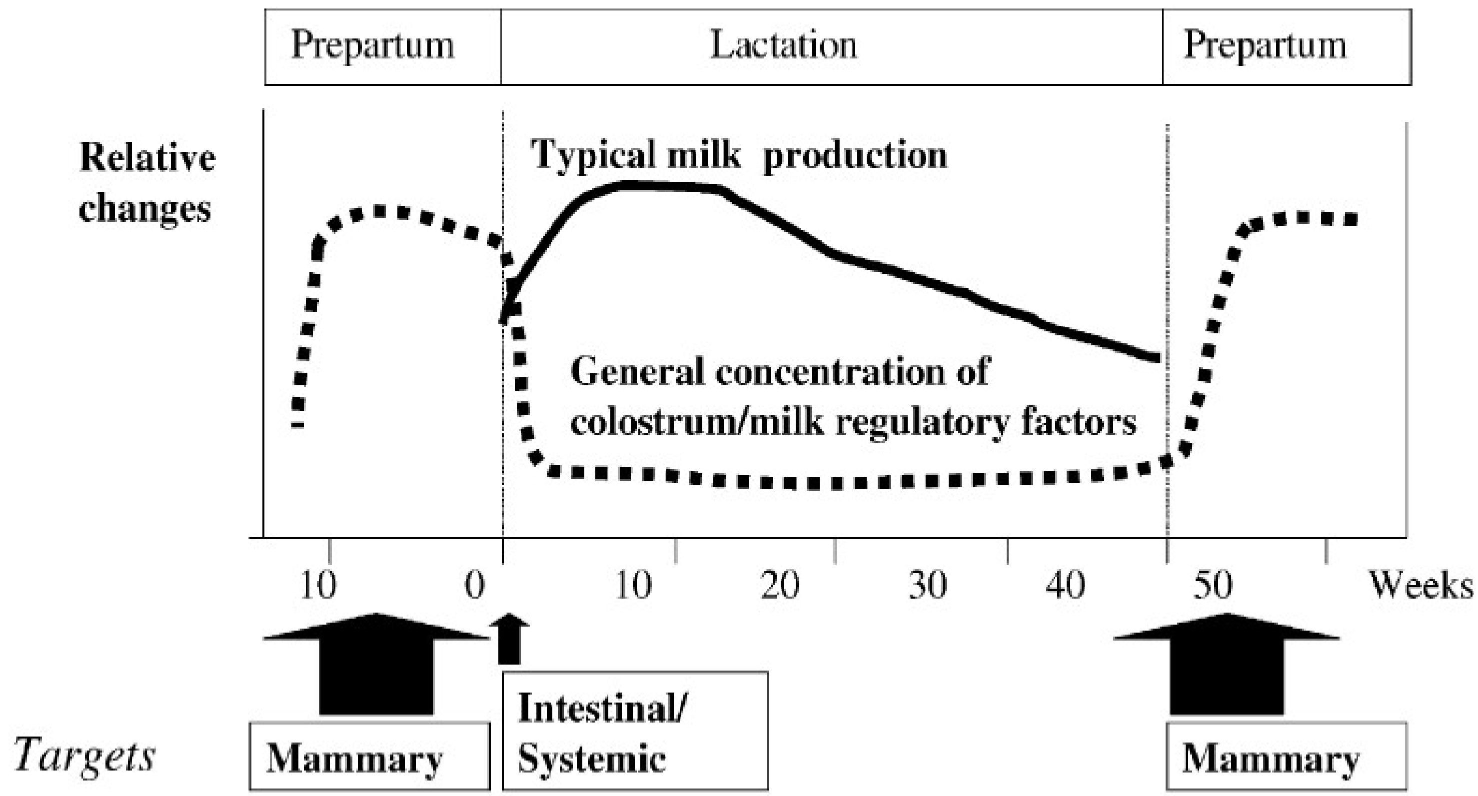


Fig. 1. Common pattern and target opportunity of regulatory/bioactive components in mammary secretions of dairy cows.

Blum and Baumrucker, 2002

Relatively new definition related to the topic of epigenetic programming in neonates:

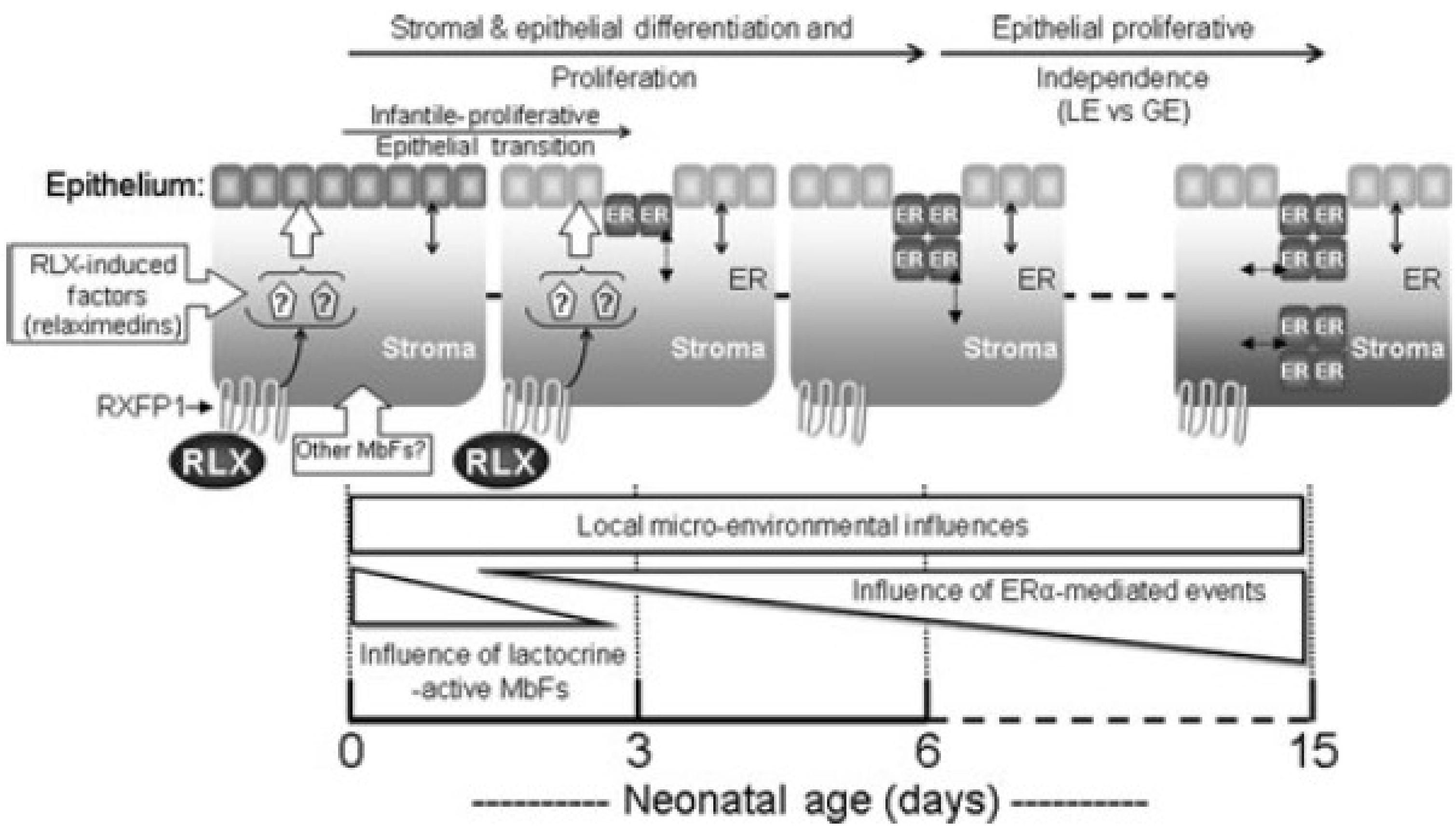
•Lactocrine hypothesis (Bartol, Wiley and Bagnell, 2009)

- maternal programming extended beyond the uterine environment through ingestion of milk-borne morphological factors - milk in this case can include colostrum

- In neonatal pigs, maternal relaxin from colostrum stimulates development and differentiation of the uterus (15 vs 30 ml colostrum)

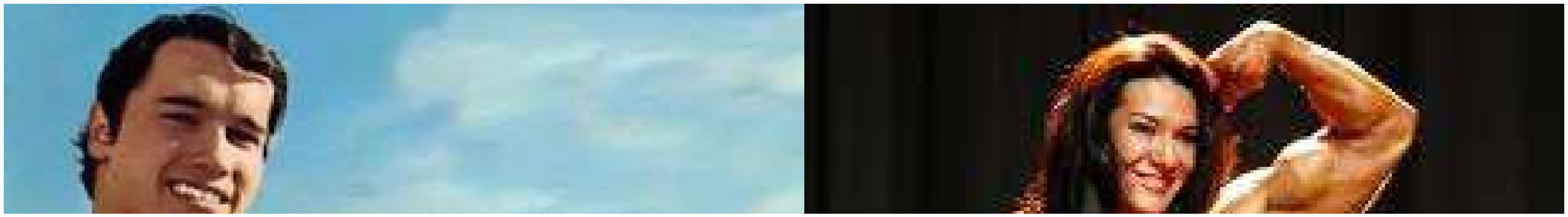
- Mediates the expression of estrogen receptors – stimulates on differentiation of stroma and epithelial cells and then proliferation

Role of colostrum Relaxin in female piglets on expression of estrogen receptors and development



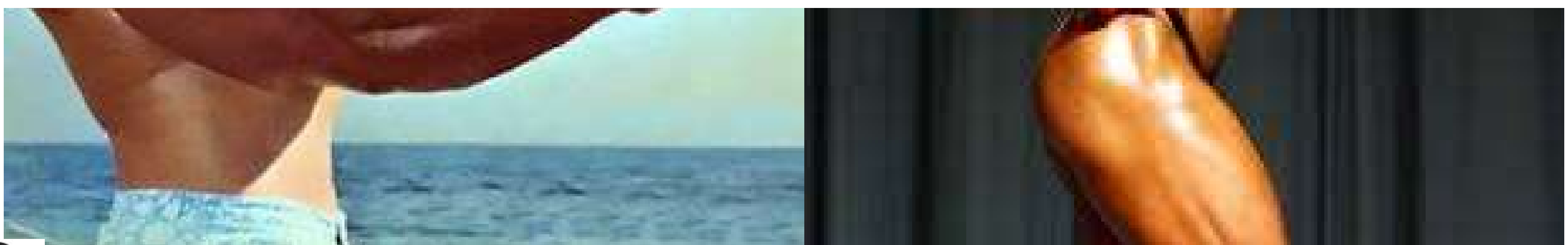
(Bartol, Wiley and Bagnell, 2008)

What Does Mom Want for Her Calf?

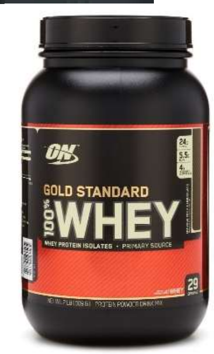


She wants them to grow and be healthy –

Anabolism!



With or without the steroids?



Colostrum vs milk

Components	Units	Colostrum	Mature Milk
Gross Energy	MJ/L	6	2.8
Immunoglobulin G	g/L	81	<2
Lactoferrin	g/L	1.84	Undetectable
Insulin	µg/L	65	1
Glucagon	µg/L	0.16	0.001
Prolactin	µg/dL	280	15
Growth hormone	µg/dL	1.4	<1
IGF-1	µg/dL	310	<1
Leptin	µg/dL	30	4.4
TGF-α	µg/dL	210	<1
Cortisol	pg/ml	1,500-4,400	710
17βEstradiol	pg/ml	1,000-2000	10-20

Blum and Hammon, 2000, Bonnet et al., 2002; Blum and Baumrucker, 2008

Composition of colostrum, transition milk and whole milk of Holstein cows

	Colostrum	Transition milk (milking postpartum)	
Parameter	1	2	3
Specific gravity	1.056	1.040	1.035
Total solids (%)	23.9	17.9	14.1
Fat (%)	6.7	5.4	3.9
Total protein (%)	14.0	8.4	5.1
Casein (%)	4.8	4.3	3.8
Albumin (%)	6.0	4.2	2.4
Immunoglobulins (%)	6.0	4.2	2.4
IgG (g/100 mL)	3.2	2.5	1.5
Lactose (%)	2.7	3.9	4.4
IGF-I (µg/L)	341	242	144
Insulin (µg/L)	65.9	34.8	15.8
Vitamin A (µg/100 mL)	295	190	113
Vitamin E (µg/g fat)	84	76	56

Foley and Otterby, 1978; Hammon et al. 2000

Importance of Colostrum Supply for the Neonate

- Colostrum provides immunoglobulins for establishing passive immunity
- Colostrum contains high amounts of nutrients, but also non-nutrient factors that support gut maturation
- Colostrum borne growth factors such as IGF-1 or hormones like insulin might act through specific receptors in the gut mucosa of the neonate to stimulate cell proliferation, cell differentiation, and protein synthesis
- Colostrum is a communication tool of the dam to direct calf development at the beginning of extra-uterine life

Inadequate Colostrum Intake Reduces Long Term Performance

Effects of Colostrum Ingestion on Lactational Performance, Prof. Anim. Scientist, 2005

Brown Swiss calves were fed 2 L or 4 L of colostrum and colostrum over another 6 to 8 feedings

	2 L	4 L
n	37	31
Daily gain, lb/d	1.76	2.2
Age at conception, mo	14.0	13.5
Survival through 2nd lact.	75.3	87.1
Milk yield through 2nd lact., lb	35,297	37,558

Source of Colostrum Replacement Important for Feed Efficiency – observable over first 29 days of life

Calves fed colostrum or a serum derived colostrum replacement demonstrated differences in feed efficiency

- **no differences in IgG status**

Variable	Colostrum		Colostrum Replacement	
	N	P	N	P
Total DMI, lb	34.5	33.1	30.1	32.1
Milk replacer DMI, lb	23.5	24.3	21.6	24.1
Starter DMI, lb	10.9	8.7	8.5	8.2
Feed efficiency,(gain:feed)	0.43	0.36	0.22	0.26
	0.40		0.24	

Jones et al. JDS 2004

INADEQUATE COLOSTRUM INTAKE DECREASES GROWTH OF CALVES ON INTENSIFIED FEEDING PROGRAMS

Johan S. Osorio and James K. Drackley

Colostrum status impacts feed efficiency but varies by level of nutrient intake

Conventional: 1.25 lb/d, 22:20
Intensified: 1.75 lb/d 7 days, 2.5 lb/d to 42 days 28:20
23% CP starter

	Conventional		Intensified	
Ig status	Poor	Good	Poor	Good
n	21	20	17	25
Mean serum IgG, mg/dL	558[a]	1,793[b]	609[a]	2,036[b]
Average daily gain, lb/d	1.17[a]	1.09[a]	1.39[b]	1.63[c]

[abc]means in same row with different letters are differ $P<0.10$

Effect of Colostrum level on Growth and Feed Efficiency

- Calves fed 4 L (+2L @12 hrs) or 2 L of pooled colostrum within one hour of birth
- Half of calves on each colostrum treatment assigned to "*ad libitum*" feeding regimen
- All calves are housed in a co-mingled pen and fed with an automatic feeder
- Daily intakes of milk replacer and weekly measures of body weight and hip heights
- Weekly blood samples

Soberon, 2011

Effect of High (4+2 L) or Low (2L) Colostrum and Ad-lib (H) Milk Replacer Intake on Feed Efficiency and Feed Intake in Pre and Post-Weaned calves (Soberon Ph.D. diss., 2011)

Treatment	HH	LH	
	Mean	Mean	Std dev
n	34	26	
IgG concentration, mg/dl*	2,746[a]	1,466[c]	98
Birth wt, lb	97	92	2
Weaning wt, lb	172[a]	159[c]	4
ADG pre-weaning, lb	1.74[a]	1.48[c]	0.06

Effect of High (4+2 L) or Low (2 L) and Ad-lib (H) Milk Replacer Intake on Feed Efficiency and Feed Intake in Pre and Post-Weaned calves

Treatment	HH	LH	
	Mean	**Mean**	**SD**
ADG birth to 80 d, lb	1.72[a]	1.45[b]	0.07
Hip height gain, birth to 80 d, cm/d	0.214[a]	0.184[c]	0.008
Total milk replacer intake, lb DM[1]*	97.8[a]	90.1[c]	2.4
Grain intake pre-weaning, lb[1]*	4.8[a]	4.6[a]	3.3
ADG/DMI, pre-weaning[2]*	0.60	0.67	0.042
ADG post-weaning[3], lb	2.4[a]	1.76[b]	0.13
DMI post-weaning[3], lb/d	6.4[ab]	5.7[c]	0.23

Colostrum components and gastrointestinal tract development

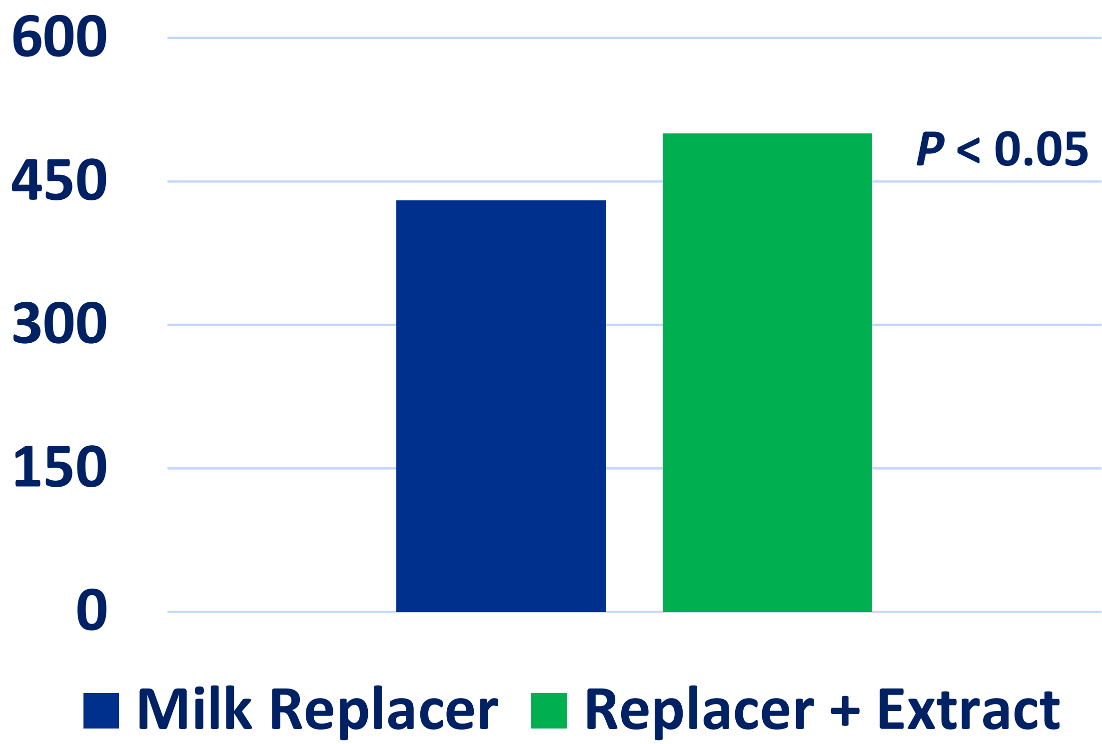
- Many studies have been conducted that demonstrate short term responses to hormones and growth factors found in colostrum
- General response is enhanced protein synthesis, increased enzyme expression, greater GIT development
- This development suggests:
  - The GIT is a stronger barrier to infection
  - Has more surface area for digestion and absorption
  - More capacity to digest more nutrients due to higher enzyme secretion

Feeding of a Colostrum Extract in Calves: Effects on Small Intestinal Villus Growth

Trait	Colostrum Extract	Colostrum 1st Milking
Gross energy, MJ/kg DM	19.7	24.9
Crude protein, g/kg DM	690	555
Immunoglobulin G, g/kg DM	44.2	159
Whey protein, g/kg DM	656	410
Crude fat, g/kg DM	3.2	265
N-free extracts, g/kg DM	173	104
Crude ash, g/kg DM	61.8	75
IGF-I, mg/kg DM	23	1.1
Insulin, μg/kg DM	365	67
Lactoferrin, g/kg DM	1.6	7.5

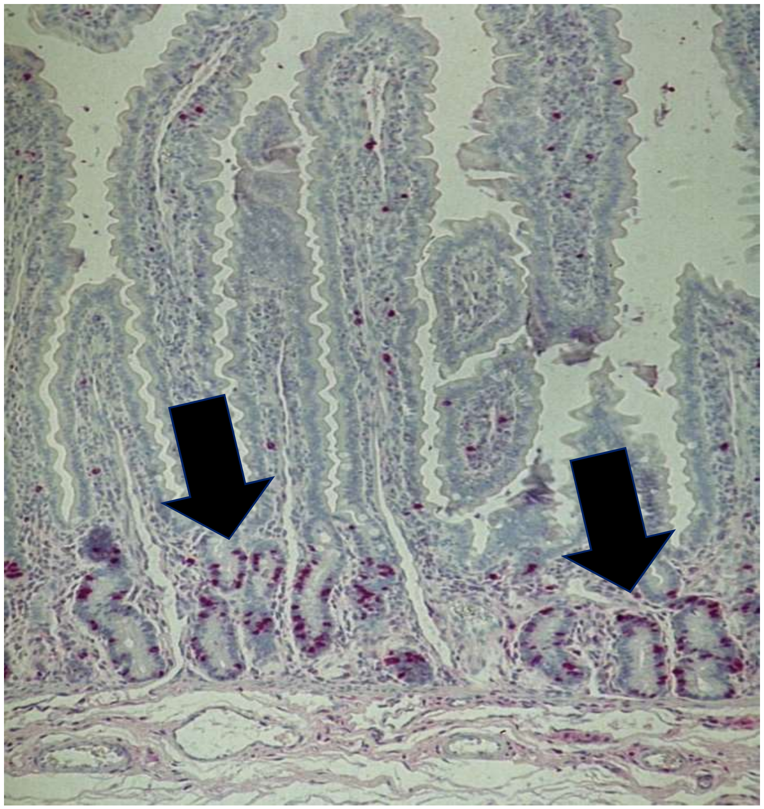
Roffler et al., 2003

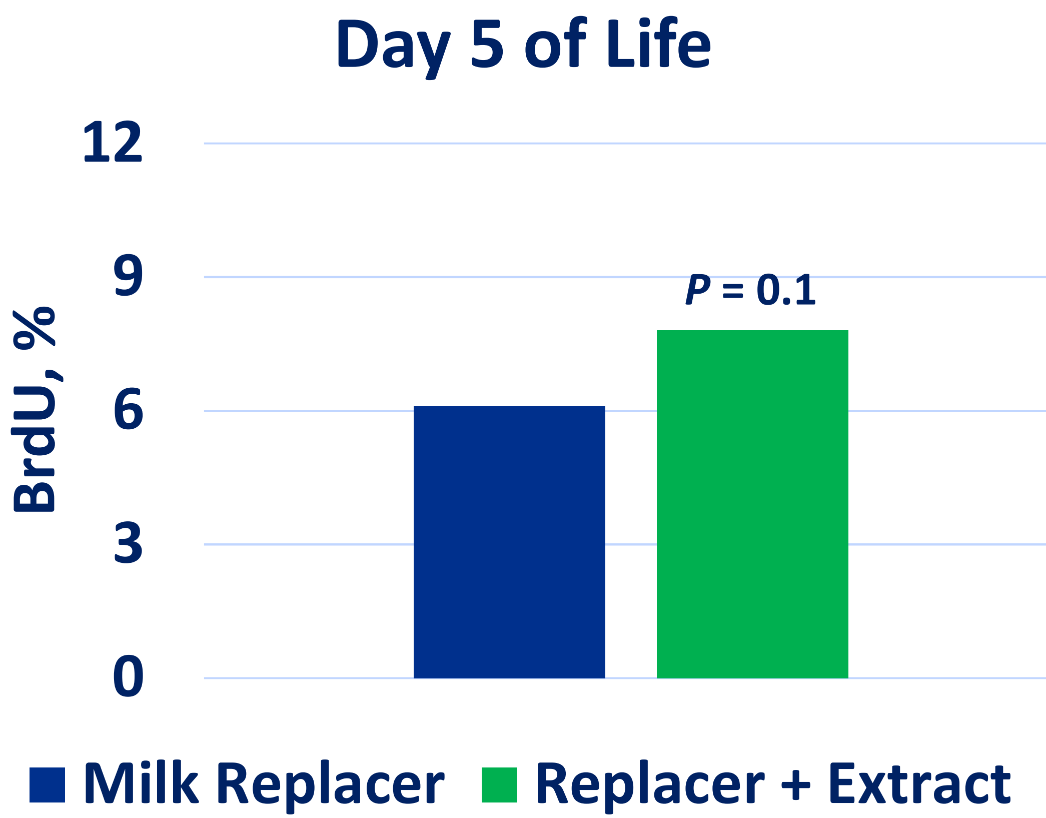
Influence on Villus Height in Neonatal Calves



Roffler et al., 2003

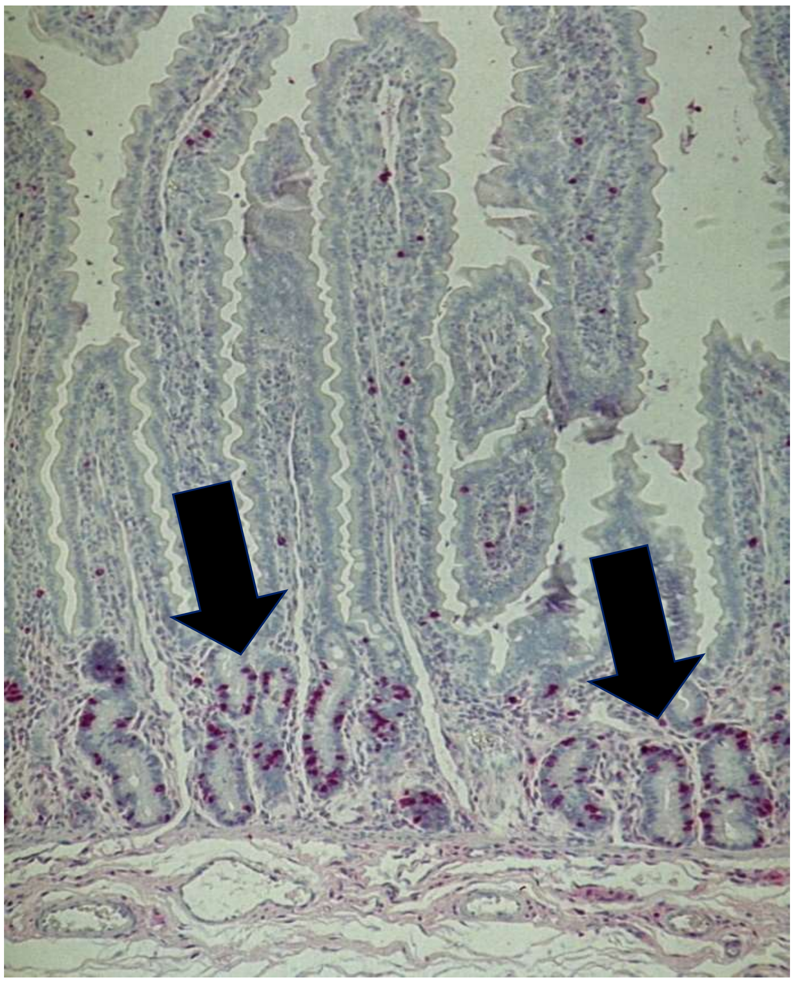
Influence on Crypt Cell Proliferation in Neonatal Calves
Milk replacer with and without a colostrum extract

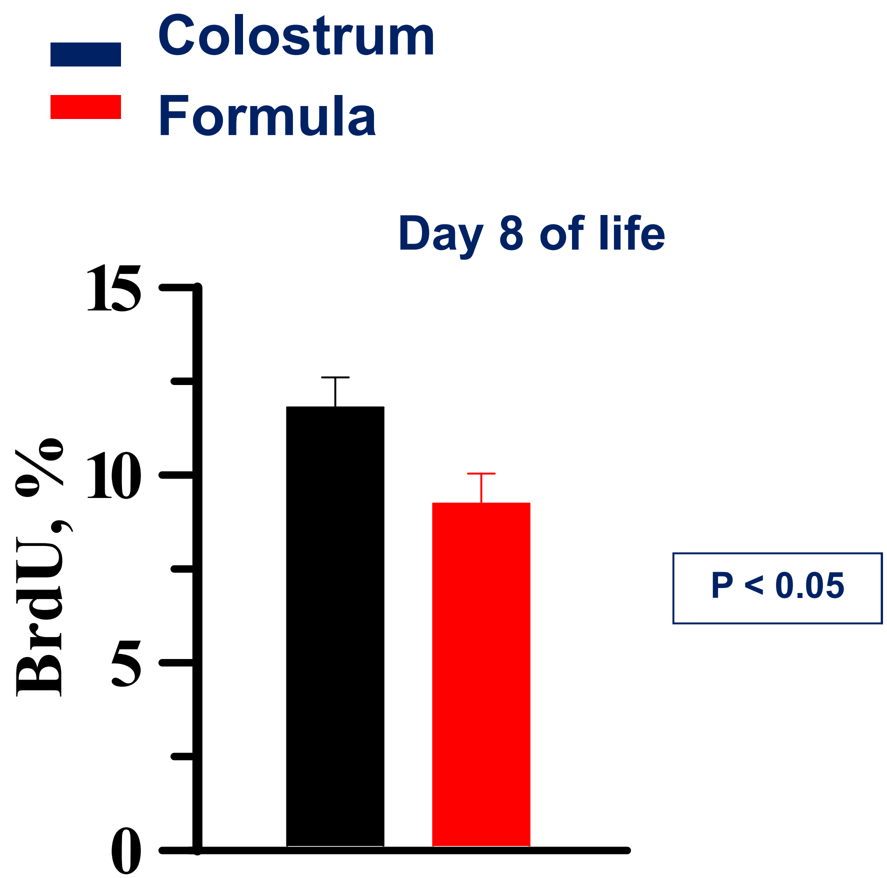




Roffler et al., 2003

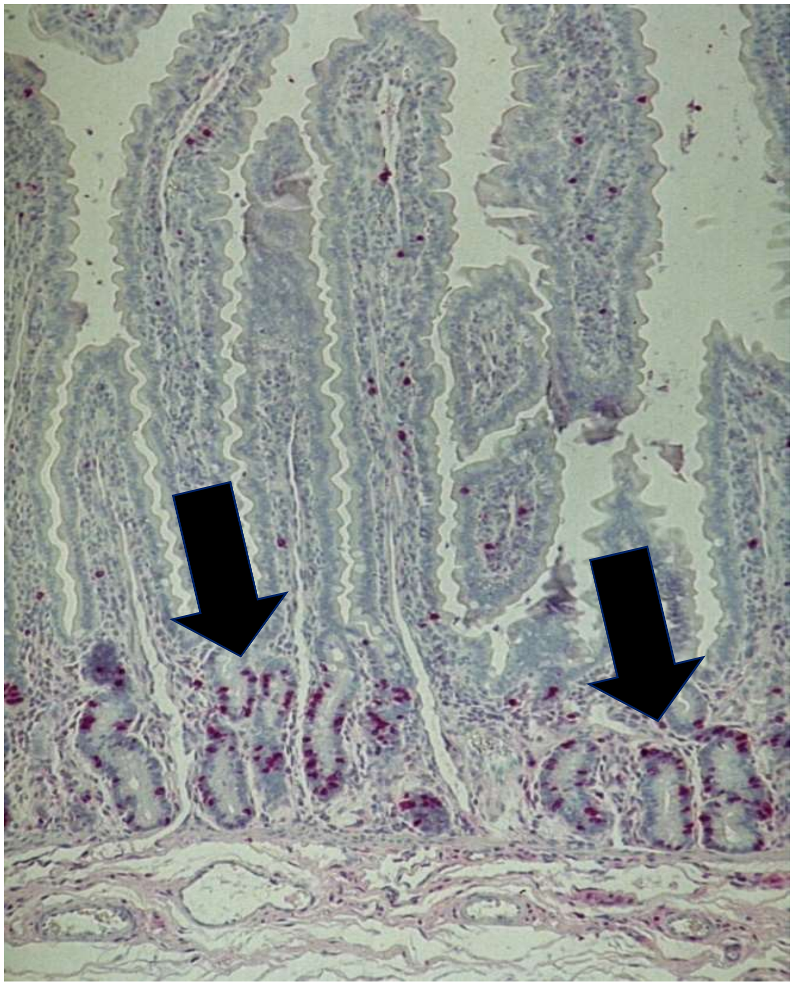
Colostrum versus Formula Feeding: Crypt Cell Proliferation in Neonatal Calves

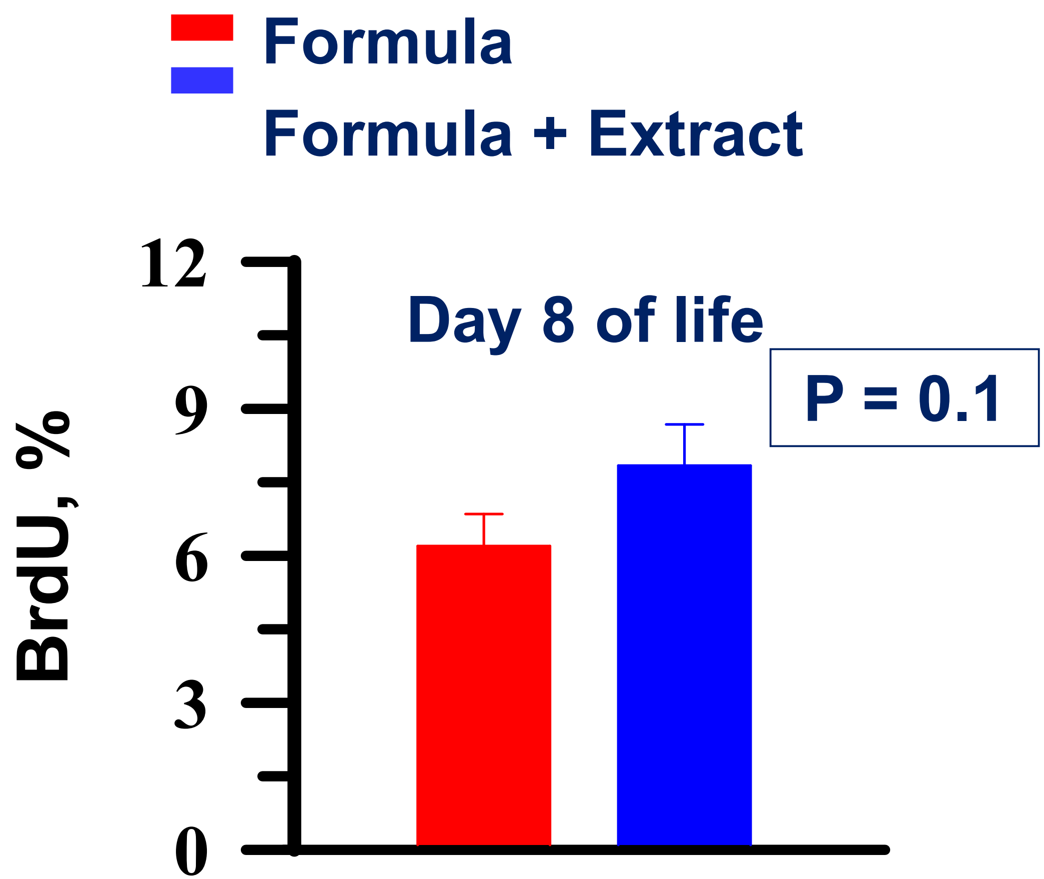




Blättler et al., 2001

Colostrum Extract Feeding:
Crypt Cell Proliferation in Neonatal Calves





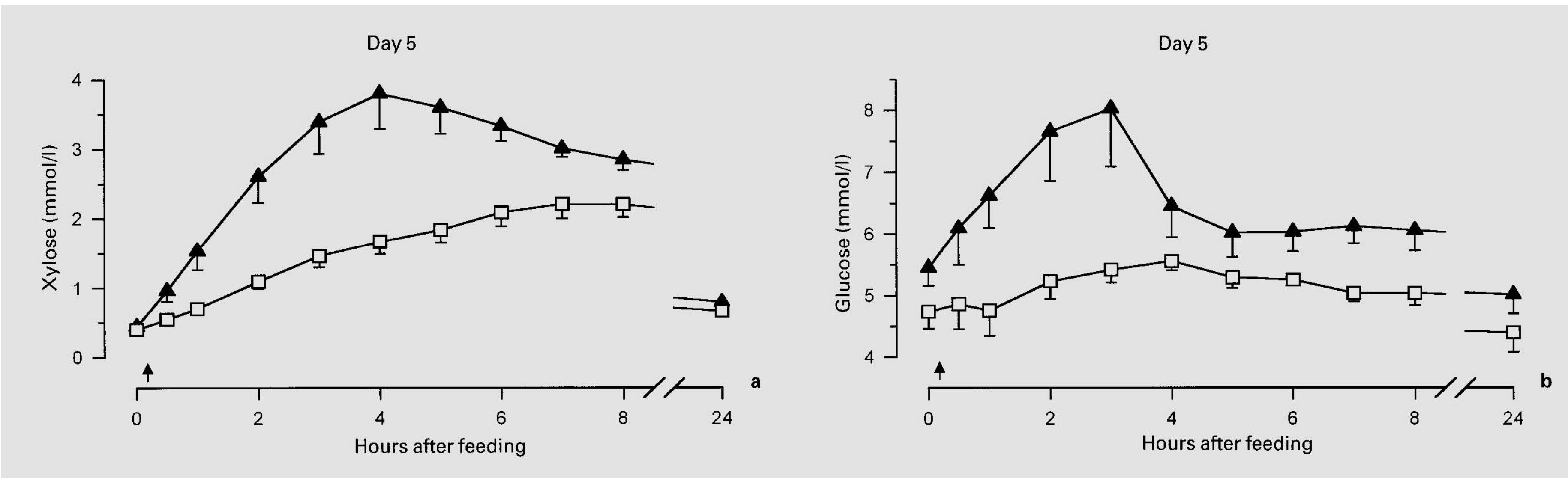
Blättler et al., 2001

Colostrum versus Formula Feeding:

Xylose Absorption in Neonatal Calves

Plasma Xylose

Plasma Glucose



▲ *Colostrum*

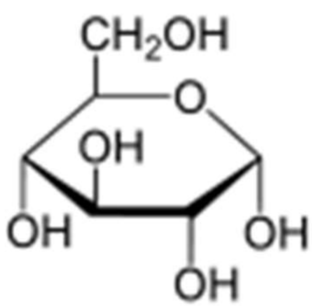
□ *Formula*

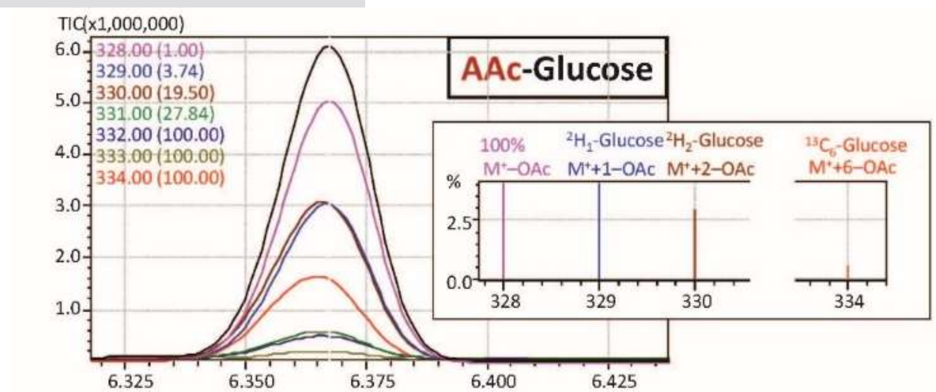
Rauprich et al., 2000

Colostrum Feeding and Glucose Uptake in Neonatal Calves

Colostrum

Formula





Steinhoff-Wagner et al., 2011

Effect of Colostrum Intake over 4 days on Glucose Metabolism and Energy Status

- 7 calves fed colostrum versus 7 calves fed milk-based formula 4 hrs on average after birth
  - Comparable in macronutrients
- Basal blood samples were drawn before morning feed and 2 hours after intake on day 1 to day 4
- Glucose absorption into blood using isotopes

Steinhoff-Wagner et al., 2011

Composition of Colostrum and Formula

	Dry Matter g/kg	Ash g/kg FM	OM g/kg FM	Lactose g/kg DM	Crude Protein g/kg DM	Crude Fat g/kg DM	Crude Energy MJ/kg DM	IGF-I µg/l
Colostrum								
Day 1	239	10.7	228.2	200.9	523.2	194.6	22.1	373.4
Day 2	179	9.1	170.0	259.6	395.9	269.1	23.6	192.4
Day 3/4	151	8.1	143.2	341.0	296.8	292.8	23.3	85.6
Formula								
Day 1	240	20.9	219.0	200.9	514.0	173.4	22.5	n.m.
Day 2	179	12.9	165.7	259.8	409.3	246.4	23.8	n.m.
Day 3/4	153	10.5	142.6	338.3	338.3	246.2	23.5	n.m.

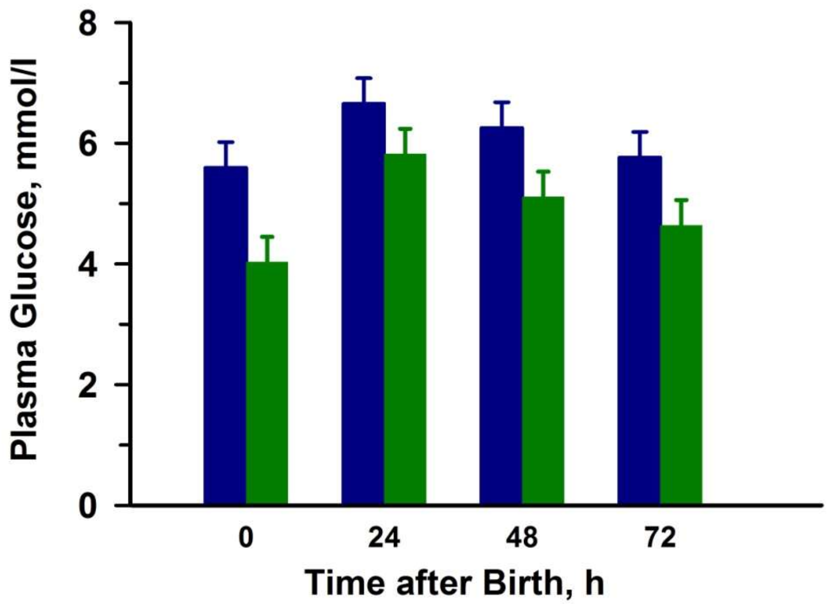
n. m. = not measureable

Steinhoff-Wagner et al., 2011

Plasma Glucose: Postnatal Concentrations and Changes after Feed Intake

Colostrum
Formula

Postnatal Concentrations before Feed Intake



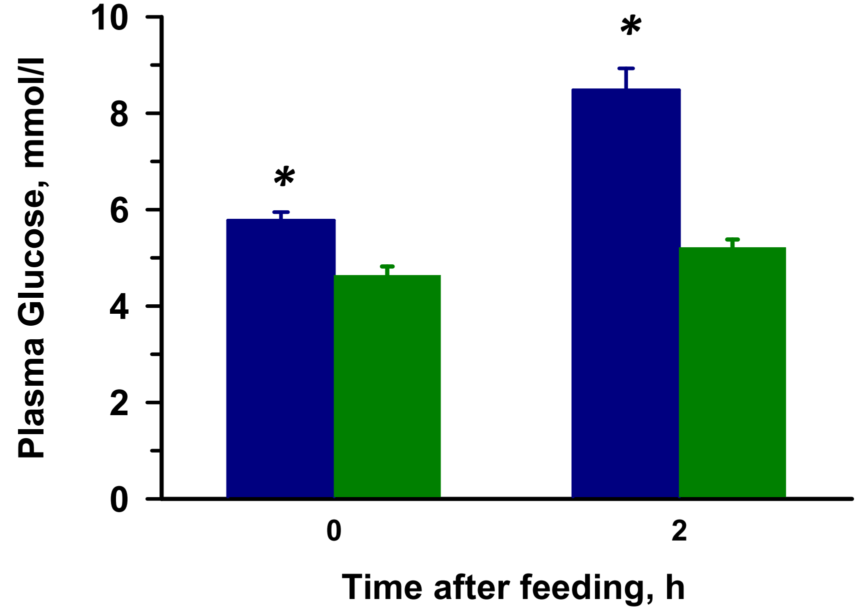
Statistics

Main Effects:

Diet	*P < 0.001*
Time	*P < 0.05*
Diet × Time	*P < 0.7*

Steinhoff-Wagner et al., 2011

Changes on Day 4 after Feed Intake



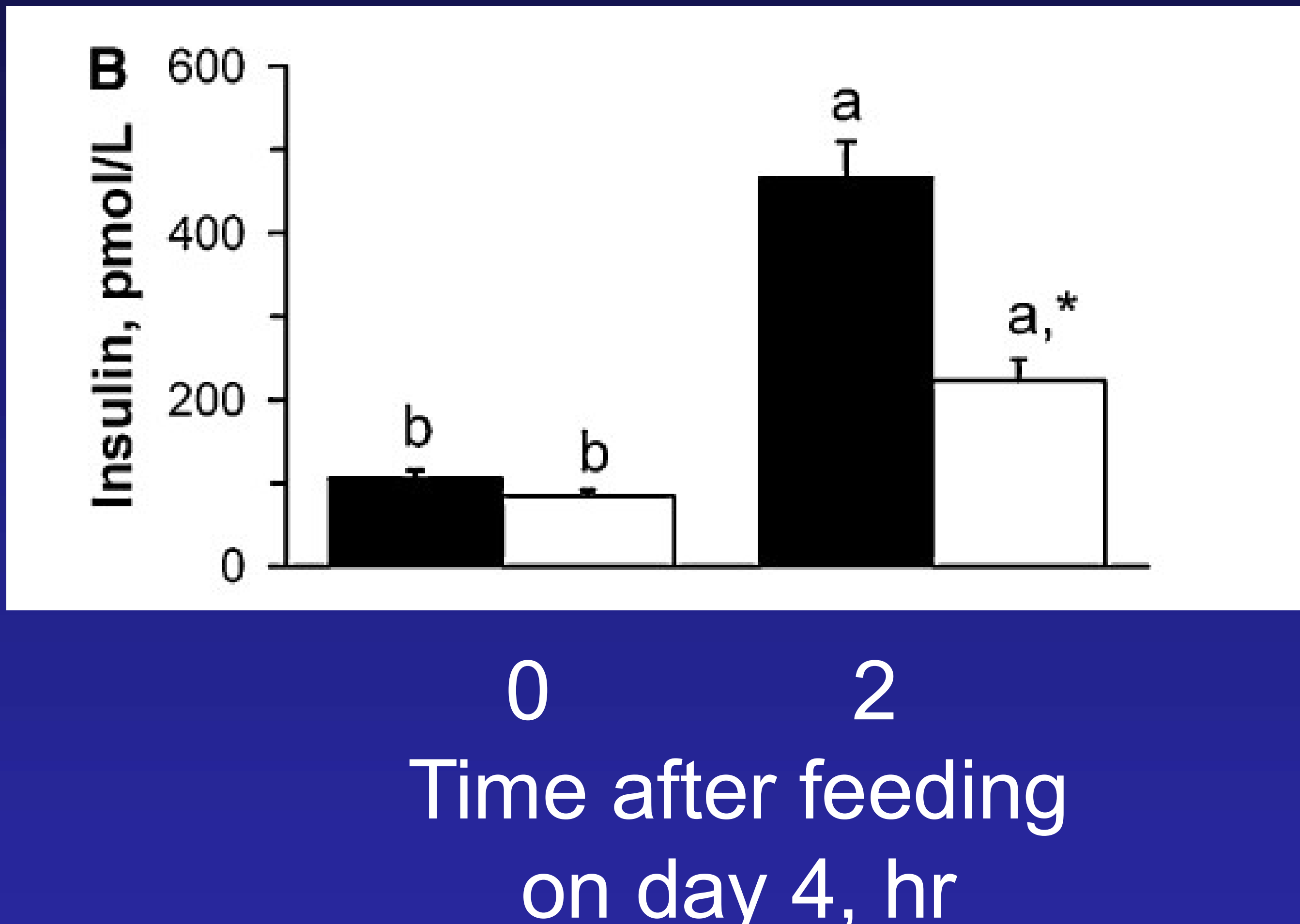
Statistics

Main Effects:

Diet	*P < 0.001*
Time	*P < 0.001*
Diet × Time	*P < 0.001*

**: Sig. Diet Effect at Time Point*

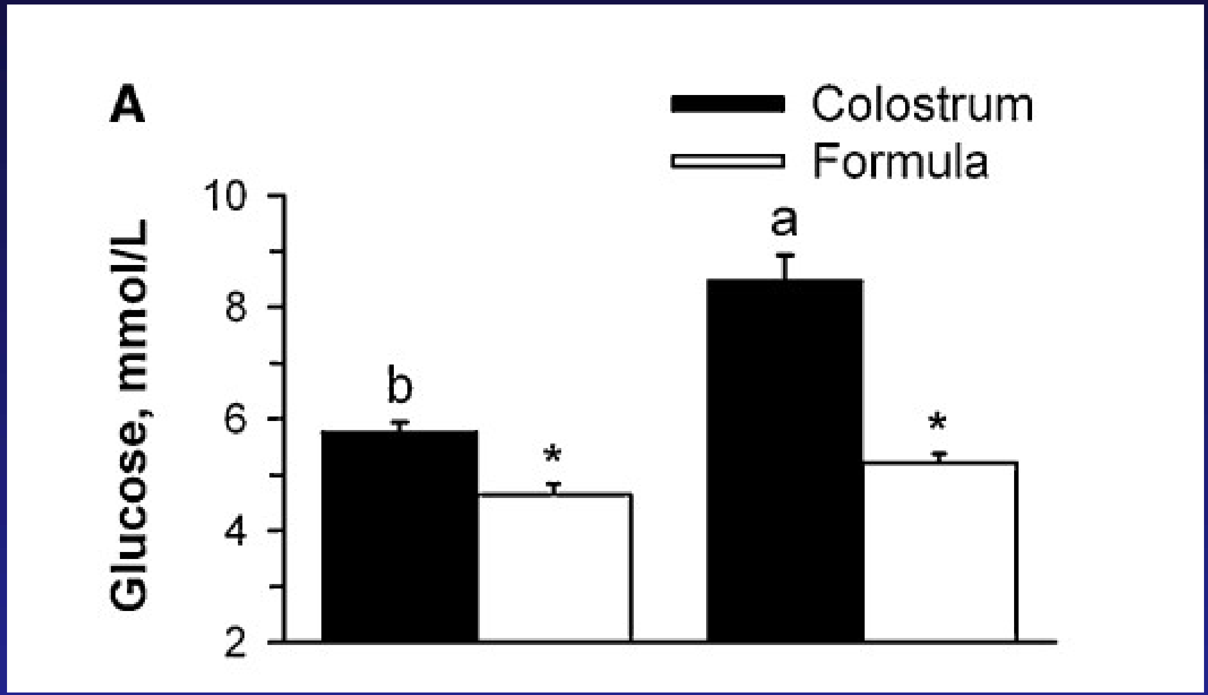
Plasma Insulin Concentration of Calves Fed Colostrum or Colostrum like formula from Birth – Day 4 of Life



Dark bars are colostrum fed calves, white bars are control calves

Steinhoff-Wagner et al., 2011

Plasma Glucose Concentration of Calves Fed Colostrum or Milk Replacer from Birth – Day 4 of Life



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Time after feeding on day 4,h

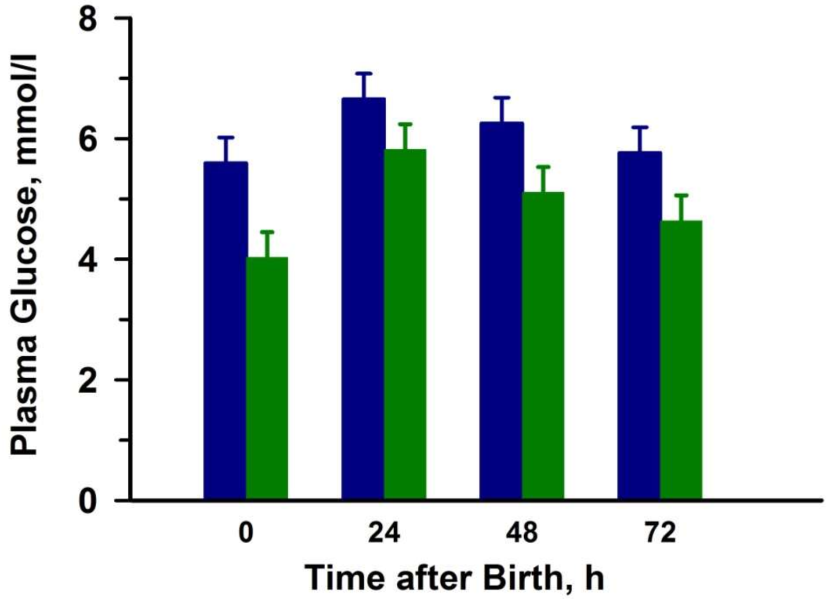
Dark bars are colostrum fed calves, white bars are control calves

Steinhoff-Wagner et al., 2010

Plasma Glucose: Postnatal Concentrations and Changes after Feed Intake

Colostrum
Formula

Postnatal Concentrations before Feed Intake



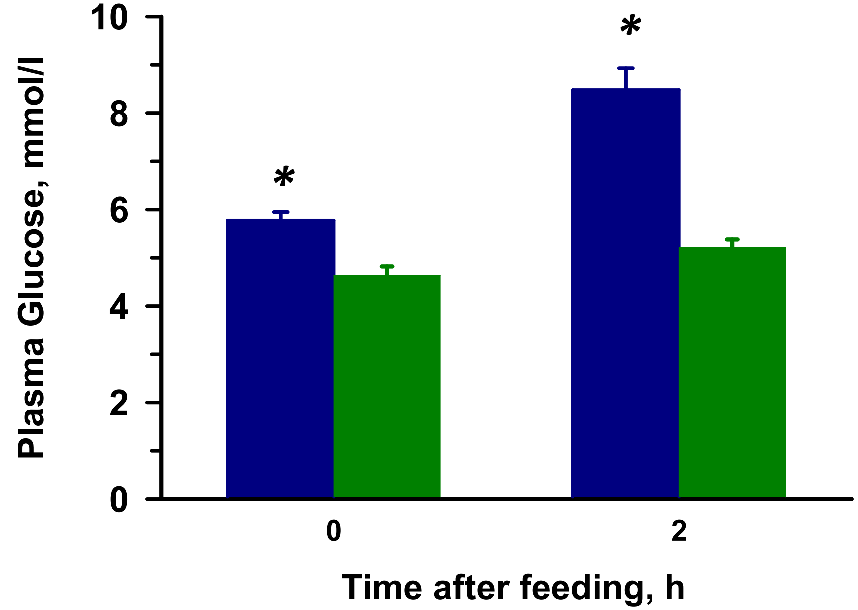
Statistics

Main Effects:

Diet	*P < 0.001*
Time	*P < 0.05*
Diet × Time	*P < 0.7*

Steinhoff-Wagner et al., 2011

Changes on Day 4 after Feed Intake



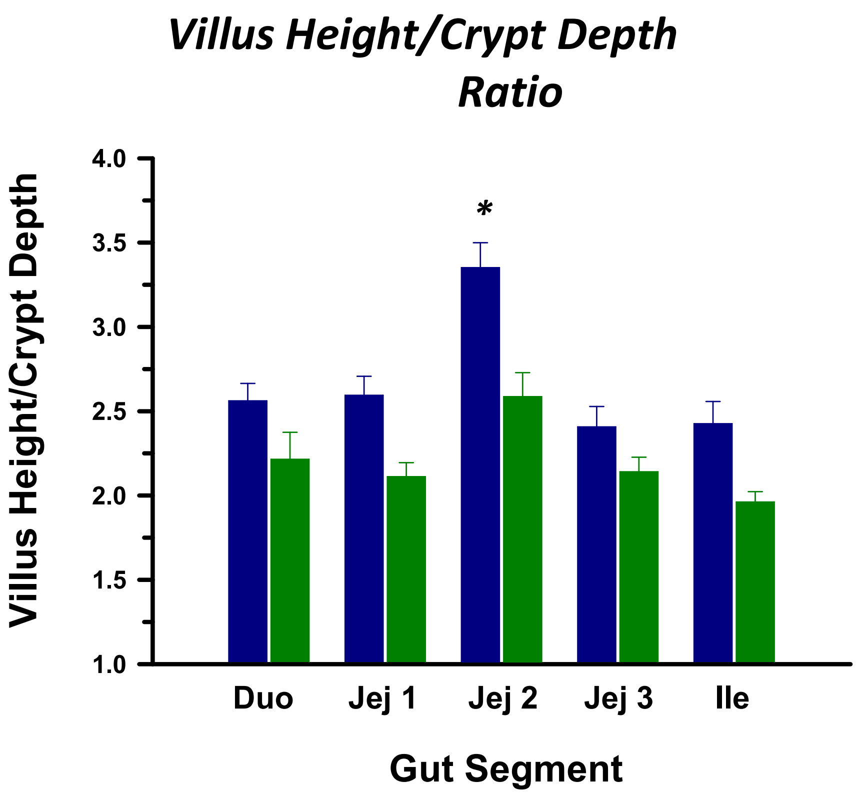
Statistics

Main Effects:

Diet	*P < 0.001*
Time	*P < 0.001*
Diet × Time	*P < 0.001*

**: Sig. Diet Effect at Time Point*

Feeding Effects on Villus Maturation and Lactase Activity in Neonatal Calves

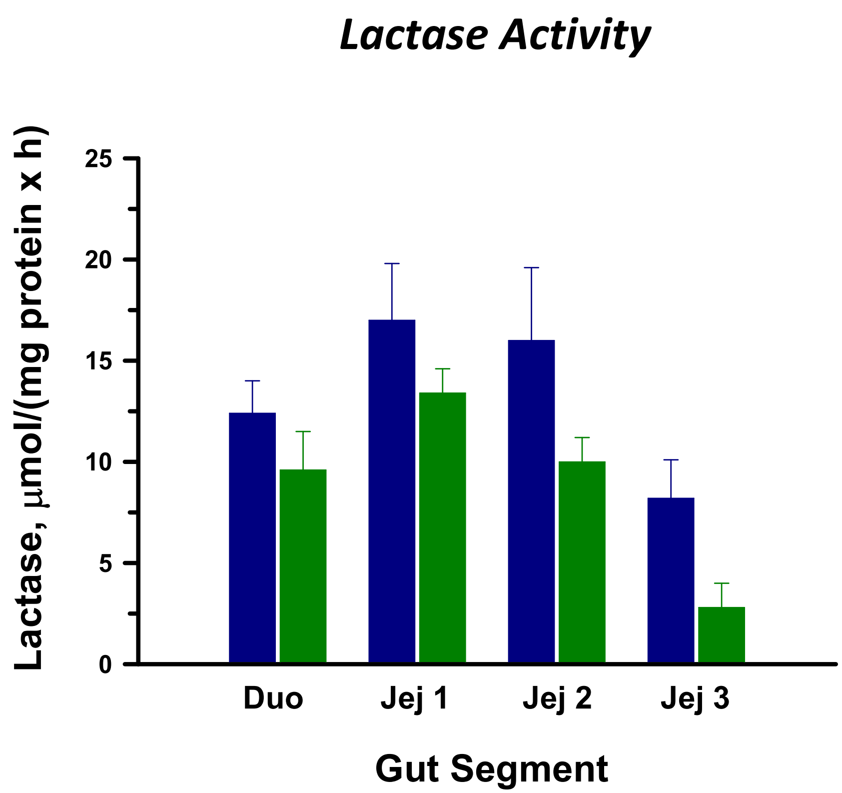


Statistics

Main Effects:

Diet	*P < 0.001*
Segment	*P < 0.001*
Diet × Segment	*P < 0.16*

**: Sig. Diet Effect in Segment*



Statistics

Main Effects:

Diet	*P < 0.06*
Segment	*P < 0.001*
Diet × Segment	*P < 0.7*

Steinhoff-Wagner et al., unpublished

Colostrum vs Milk Replacer for first 4 days of life - summary

Glucose uptake increased – similar nutrient supply
Colostrum enhanced glucose uptake via insulin or enhanced enzyme activity in gut or simply maturation of gut

Plasma glucagon higher – better glucose status, indication of higher reserve capacity

Plasma protein levels higher – more protein available for growth, higher protein synthesis, less protein for glucose

Plasma urea lower – less protein turnover and lower protein utilization for glucose production

Steinhoff-Wagner et al., 2011

Effect of Insulin Supplementation of a Colostrum Supplement on Insulin Absorption and Glucose Uptake

- 6 bulls and 6 heifers, were obtained from the Teaching and Research Dairy in Harford New York.
- Calves were dried, weighed, and received IV catheters before first feeding and a blood sample was taken immediately prior to first feeding
- Land O' Lakes Colostrum Replacer was used as colostrum, and calves were fed on average 1.25 hr after birth.
- 1000 IU of human insulin (Novolin) was added to the treatment group 1st feeding

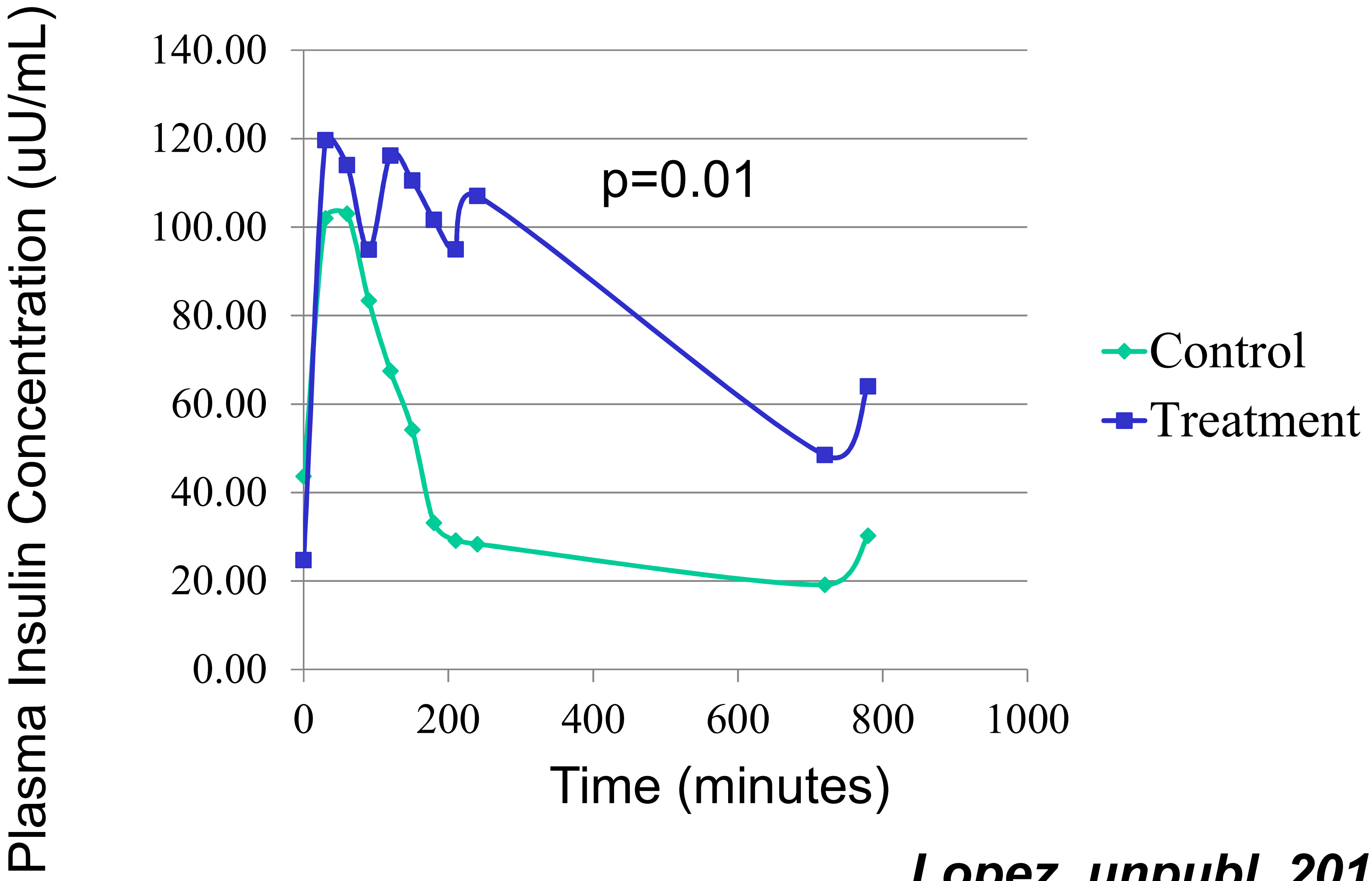
Lopez, unpubl. 2012

Sampling

- Samples were obtained every 30 minutes for the first 4 hours from the catheter following first feeding
- Calves were fed their second feeding (colostrum replacer) 12 hours post first feeding
- Final samples were obtained immediately before and 1-hour after second feeding

Lopez, unpubl. 2012

Insulin Curves



Lopez, unpubl. 2012

Plasma Glucose and Insulin of Calves Provided Supraphysiologic levels of Insulin in a Colostrum Replacer

	Control	Treatment	S.E.	P
Insulin, uU/ml	56.75	85.45	7.99	0.01
Glucose, mg/dL	69.81	81.74	3.56	0.02

Lopez, unpubl. 2012

What happens to immune cells in colostrum?

- Data generated over the last 15 -20 years demonstrates that leukocytes and other immune related cells in colostrum are “trafficked” into circulation in the calf

- Does this have any impact on the activity of the neonatal immune system?

- Other implications for the calf?

Immune cell transfer from colostrum to circulation

- Maternal leukocytes can be detected in calf circulation within 12 hr, peak at 24 hr and disappear by 48 hr. (Reber et al. 2008)
- Cells appear to be sequestered into tissues and lymph nodes after 48hr (Tuboly and Bernath, 2002; Williams, 1993).
- However, cells have been measured up to 5 wks after colostrum administration (Reber, et al. 2005)
- Long-term there appears to be greater cellular immunity in calves that received the whole colostrum compared to cell free colostrum (Reber et al. 2005; 2008)

Immune cell transfer from colostrum to circulation

- Calves fed whole colostrum have greater cellular immunity as defined the activation markers CD25 and CD26 by 7 days after birth

- Also greater antigen presenting capacity on cell surfaces

- Calves fed whole colostrum have greater cellular immune responsiveness to vaccinations

Reber et al. 2008

Effect of maternal cells transferred with colostrum on cellular responses to pathogen antigens in neonatal calves

- Calves were fed whole colostrum, frozen colostrum, or cell-free colostrum within 4 hours after birth.
- Leukocytes were obtained from calves before feeding colostrum and 1, 2, 7, 14, 21, and 28 days after ingestion.
- Proliferative responses against bovine viral diarrhea virus (BVDV) and mycobacterial purified protein derivatives were evaluated.
- Dams received a vaccine containing inactivated BVDV, but were not vaccinated against mycobacterial antigens.

Donovan et al. 2007. Am J Vet Res. 68:778–782

Effect of maternal cells transferred with colostrum on cellular responses to pathogen antigens in neonatal calves

- All calves had essentially no IgG in circulation at birth, but comparable and substantial concentrations by day 1.
- Calves that received whole colostrum had enhanced responses to BVDV antigen 1 and 2 days after ingestion of colostrum.
- Calves that received frozen colostrum or cell-free colostrum did not respond to BVDV.
- No difference in mycobacterium challenge in all treatments
- **Take home:** uptake of cells from colostrum enhance cellular immunity in calves by providing mature, programmed cells from the dam

Donovan et al. 2007. Am J Vet Res. 68:778–782

Take home for colostrum management

Colostrum feeding for 4 days….

First milking colostrum within 6 hr of birth – 4 qt for large breeds

First milking colostrum at 12 hr

Second milking colostrum for day 2

Third and fourth milking colostrum for days 3 and 4

Summary

- Mom is trying to send information to the calf via mammary secretions – some of our management approaches have short circuited this "information flow"

- Colostrum contains factors that impact intestinal development and nutrient supply independent of nutrient consumption

- Colostrum can positively impact pre and post weaning feed efficiency (from 12 to over 50%)

- The dam makes colostrum for more than one day, and this has additional impacts on calf development

Thank you for your attention