Pathways to improved fertility

Do we all speak the same language?

Jo Leroy
DVM, PhD
Jo.leroy@uantwerpen.be

In this talk …

- Energy metabolism and fertility: focusing on what really matters
- Fertility … the deep dive
- How to set optimal metabolic health and fertility:
  - Go for a healthy cow!
  - CCP's for fertility … the real list!
  - Feeding for fertility? Yes, we can!
- Conclusions

Bovine reproduction in HACCP terms

In a METABOLICALLY HEALTHY cow!

Our end product:

1) Healthy
2) Every year
3) Genetic gain
4) Future producers

The female calf becomes your future cow!

Colostrum intake → milk feeding → weaning → growth curves → age of breeding → age of first calving → ease of first calving → milk production and performances → metabolic health and ***fertility***

Heifer rearing = 25% of dairy farm's cost!

Calving

Calving conditions dramatically affect:
1) Milk production
2) Future reproductive performance

Optimal calving management should focus on:
1) Hygiene, cow comfort and calving process
2) Appetite and DMI of the cow

Successfull reproduction?

observation
DMI
transition
housing
Genetic merit
AI management
Energy balance
disease
data management
calving
Dry period
hygiene
Heifer rearing
stress
environment
Reproductive physiology
Farm type
Strategy and priorities
ration

Misconception 1

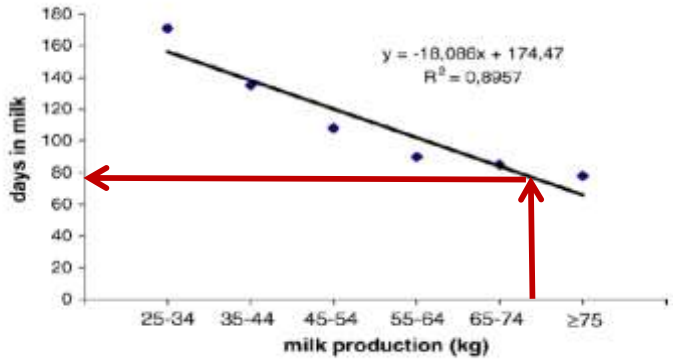


Fig. 1. Days in milk at conception according to the milk production at Day 50 postpartum.

Is the cow <u>adapted</u> to the management and
is the management <u>adapted</u> to the cow?

Is the dairy cow adapted to the "modern" management?

Is the management adapted to the modern dairy cow?

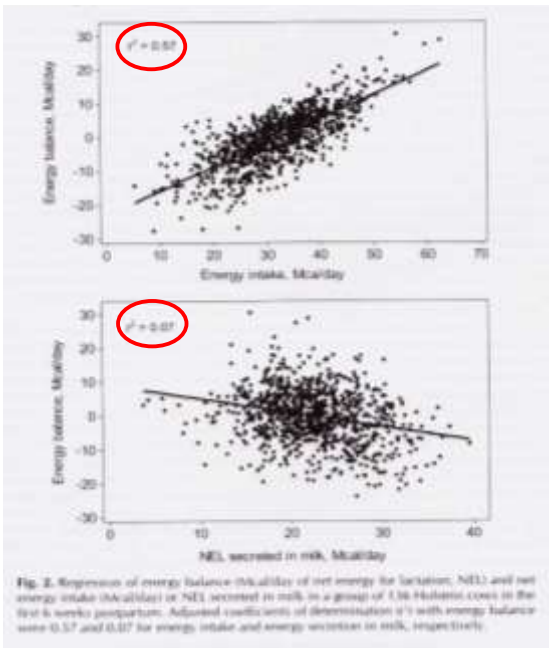
Think First before you start expensive fertility treatments!

Negative energy balance is …

1) **Dry matter intake**, energy intake
   - **If** they (can) eat
   - **When** they eat
   - **What** they eat

1) **Metabolic energy priority**
   - Energy is first used by …
   - Energy availability in the body

Energy balance and DMI



IF…

Santos et al., 2010

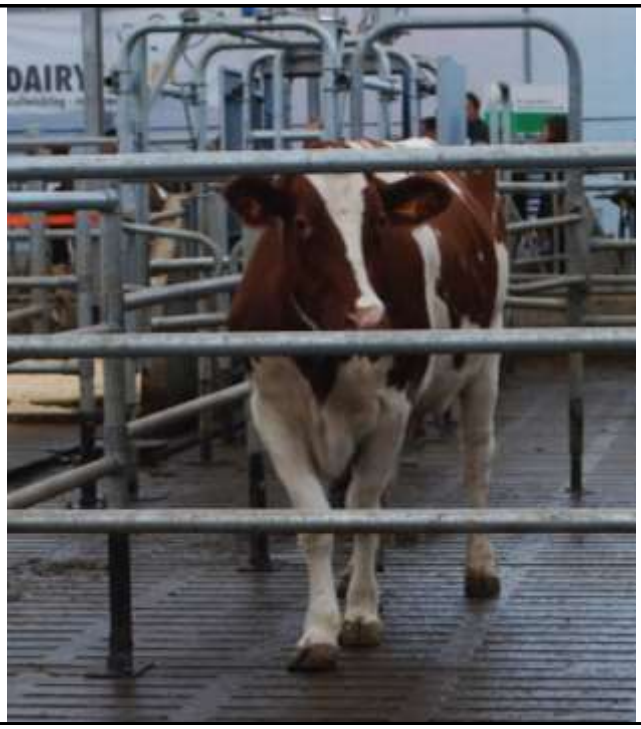
So … what is the most important concept when speaking about EB management?

Energy uptake!

Cows must be able to eat:

IF…

- health
- ration
- composition
- quantity
- taste
- digestibility
- competition
- availability
- freshness
- reachable



IF…

appetite?? Dry matter intake?

WHEN

Never speak about ENERGY BALANCE without discussing APPETITE first!

Never speak about APPETITE without discussing DRY COW MANAGEMENT first!

The energy balance early postpartum needs to be PREPROGRAMMED and cannot be adjusted in real time (too late)!

DRY COW MANAGEMENT

So … what is the most important concept when speaking about ER management?

Energy uptake!

Cows must be able to eat:

WHEN

BODY CONDITION

ration

composition

taste

digestibility

quantity

competition

availability

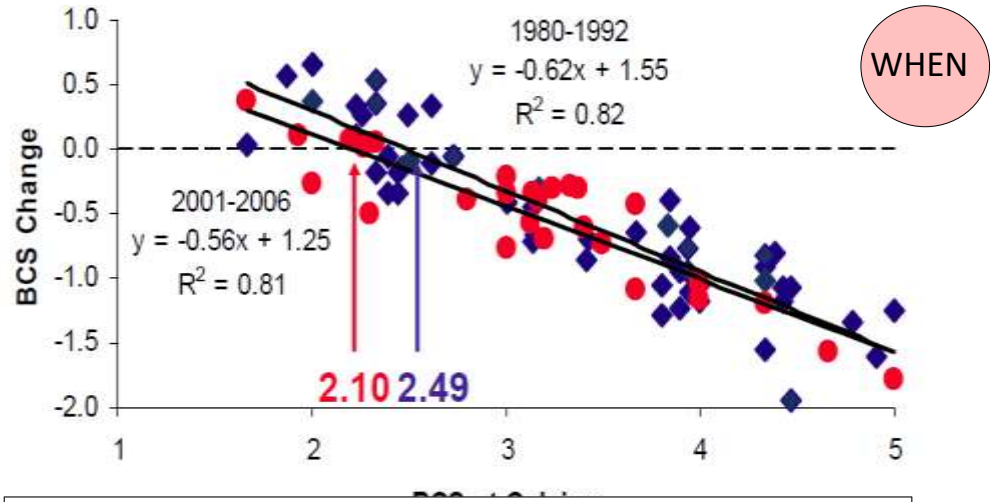
freshness

reachable

DRY COW MANAGEMENT

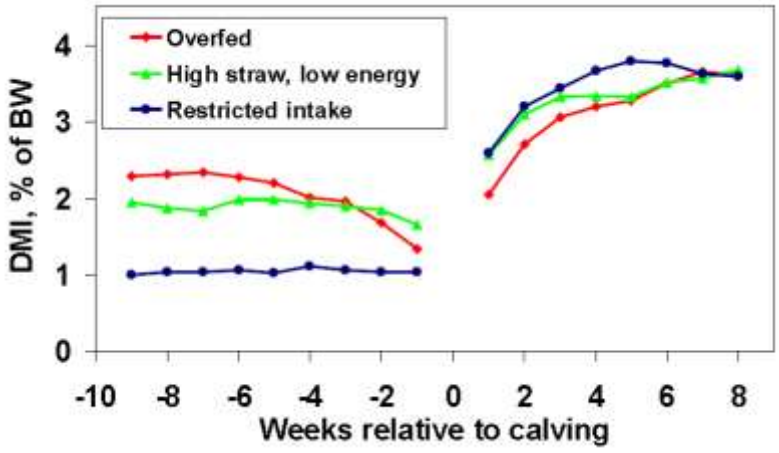
Dairy cows account on body reserves to guarantee milk production!

Loss of body condition is correlated with health problems and reproductive outcome

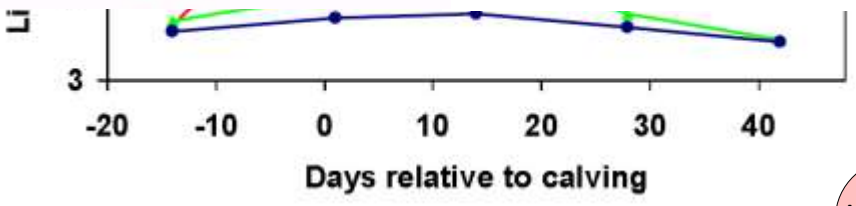


BCS change is negatively correlated with the cow's ability to ADAPT (by doing what?).
BCS change is positively correlated with the cow's vulnerability to malfunction and disease.

WHEN



Janovick Guretzky and Drackley, 2006



Janovick Guretzky and Drackley, 2006

WHEN

WHEN

Taken together:

LAST TRIMESTER of previous lactation is major driver of dry cow BCS

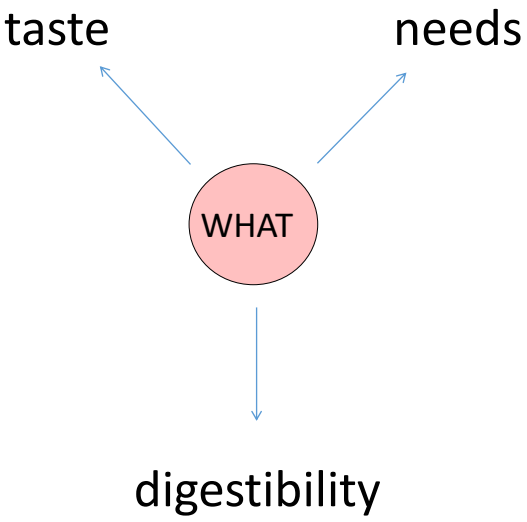
DRY COW BCS and MANAGEMENT is a major driver of appetite early lactation

Early lact.

Dry

APPETITE and thus DMI is the major driver of metabolic health!

Higher NEFA is increased risk for DA, fatty liver, fertility issues

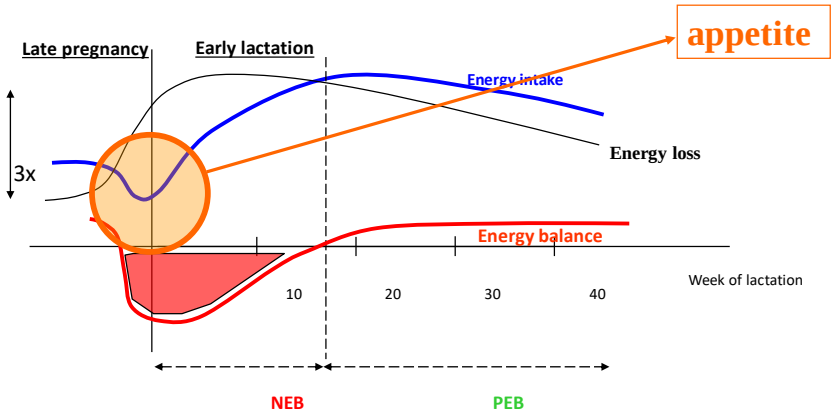


Negative energy balance is …

1) **Dry matter intake**, energy intake
   - **If** they (can) eat
   - **When** they eat
   - **What** they eat

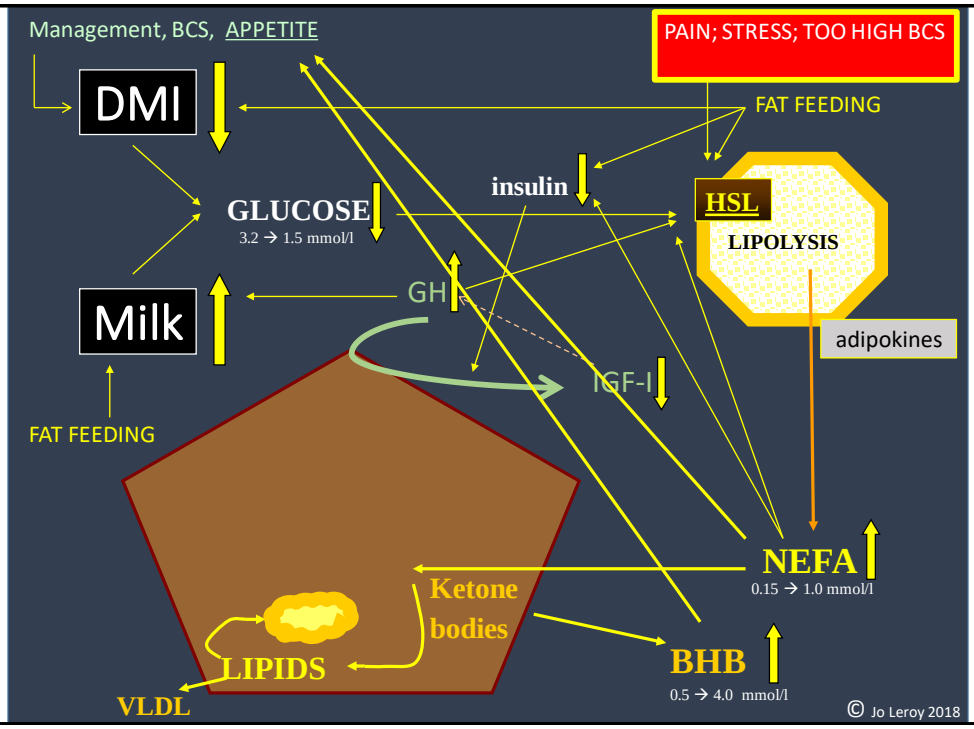
1) **Metabolic energy priority**
   - Energy is first used by …
   - Energy availability in the body

Fetus and udder have absolute priority on glucose consumption → lower blood glucose



The duration, the depth and the timing are important in terms of diseases, milk production and fertility

Bossaert et al., 2008



In this talk …

- Energy metabolism and fertility: focusing on what really matters
- Fertility … the deep dive
- How to set optimal metabolic health and fertility:
  - Go for a healthy cow!
  - CCP's for fertility … the real list!
  - Feeding for fertility? Yes, we can!
- Conclusions

Maternal health and dairy cow fertility: more than only nutrition!

Estrus cyclicity

Pregn at first AI

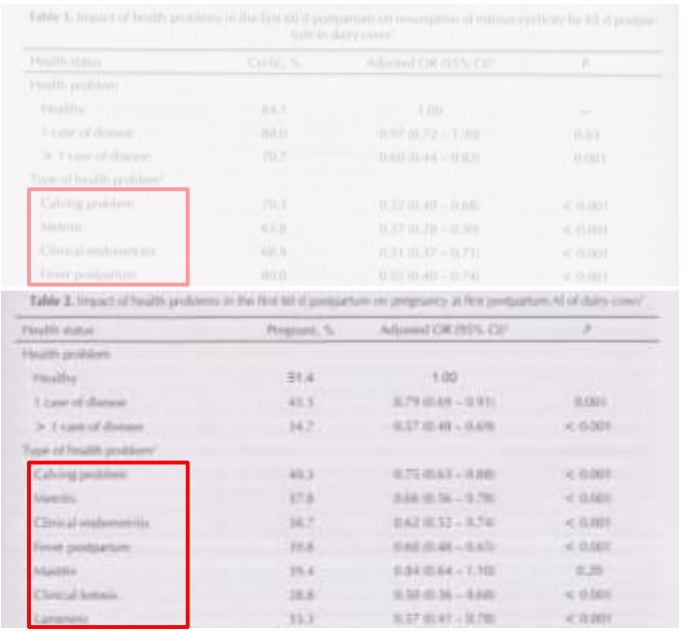


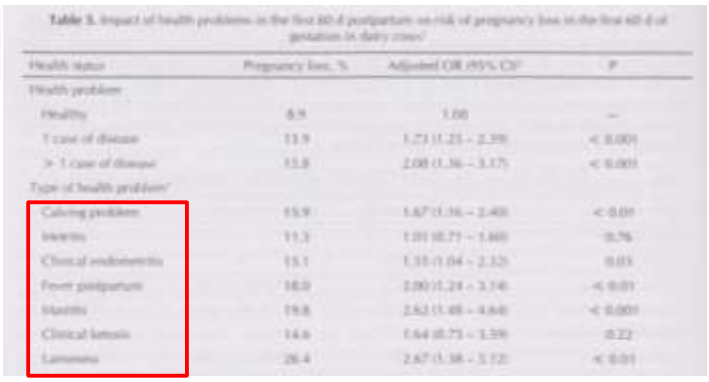
Table 2. Impact of health problems in the first 60 d postpartum on pregnancy at first postpartum AI of dairy cows[1]

Health status	Pregnant, %	Adjusted OR (95% CI)[2]	P
Health problem			
Healthy	31.4	1.00	
1 case of disease	45.3	0.79 (0.69 – 0.91)	0.001
> 1 case of disease	34.7	0.57 (0.48 – 0.69)	< 0.001
Type of health problem[3]			
Calving problem	40.3	0.75 (0.63 – 0.88)	< 0.001
Metritis	37.8	0.66 (0.56 – 0.79)	< 0.001
Clinical endometritis	36.7	0.62 (0.52 – 0.74)	< 0.001
Fever postpartum	39.8	0.68 (0.48 – 0.67)	< 0.001
Mastitis	39.4	0.84 (0.64 – 1.10)	0.20
Clinical ketosis	28.8	0.50 (0.36 – 0.68)	< 0.001
Lameness	33.3	0.57 (0.47 – 0.70)	< 0.001

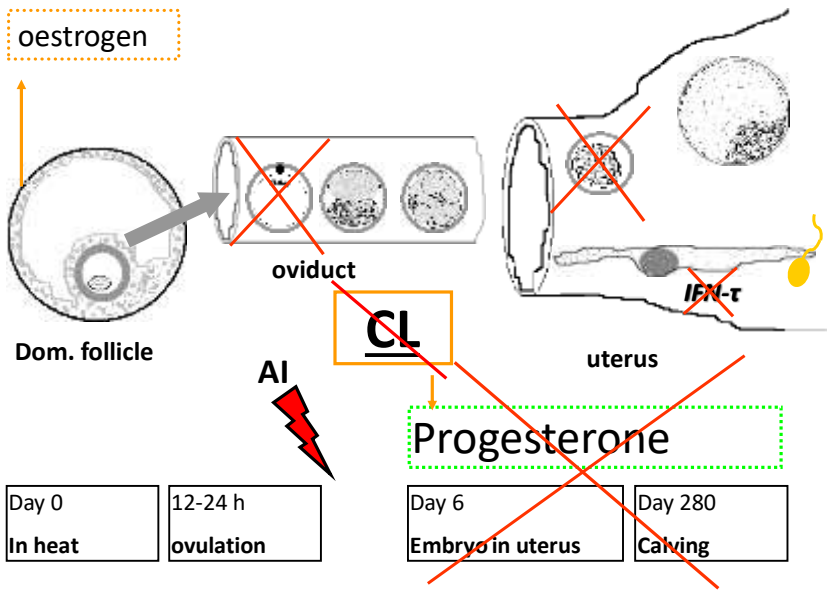
Santos et al., 2010

Maternal health and dairy cow fertility: more than only nutrition!

Pregn loss in first 60d



Santos et al., 2010



Oocyte quality:

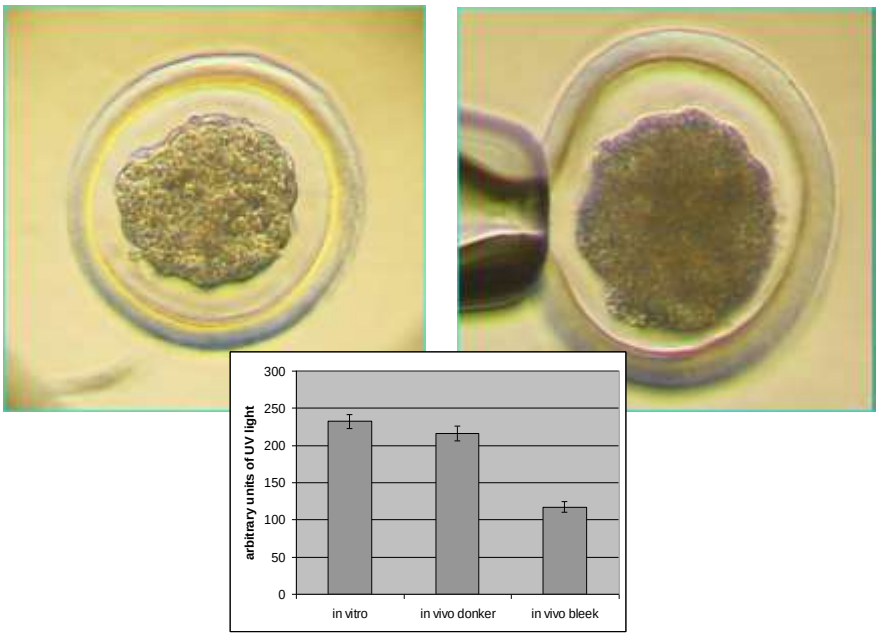
Conception	90%
Early embryo mortality	40%
Late embryo mortality	20%
Foetal loss	5%
Perinatal calf mortality	8%

100 AI's

↓

38 calves

Importance of oocyte, embryo and corpus luteum quality



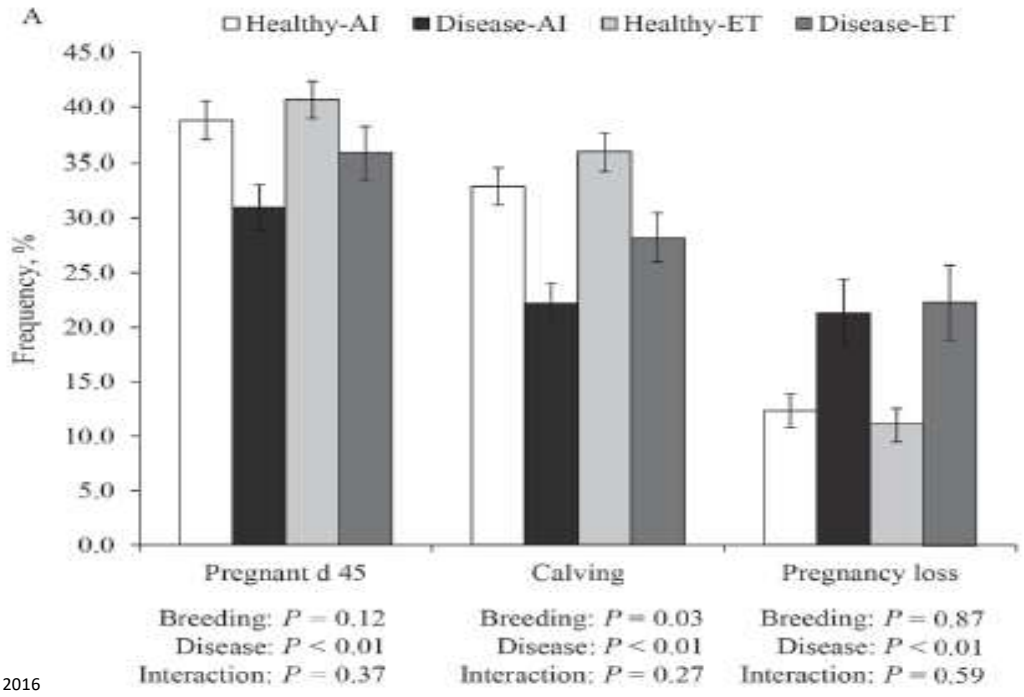
Does the oocyte has a memory?

Table 7. Embryo characteristics of lactating Holstein cows based on BW change from first to third week postpartum (values presented as mean ± SEM)

Item	Quartile group[1]				
	Lost BW+: fourth quartile	Lost BW: third quartile	Maintained BW: second quartile	Gained BW: first quartile	*P*-value
Corpora lutea (no.)	18.4 ± 2.6	18.4 ± 1.7	19.0 ± 1.7	16.0 ± 2.0	0.67
Total ova/embryos (no.)	9.6 ± 2.5	10.6 ± 1.7	6.4 ± 1.2	7.4 ± 1.4	0.31
Fertilized structures (no.)	7.6 ± 2.1	7.3 ± 1.1	4.8 ± 1.1	5.8 ± 1.4	0.43
Degenerated embryos (no.)	2.7 ± 0.7^{a}	1.7 ± 0.7^{ab}	0.7 ± 0.2^{b}	0.6 ± 0.2^{b}	0.02
Quality 1 and 2 (no.)	4.2 ± 1.4	5.3 ± 0.9	3.9 ± 1.1	4.9 ± 1.4	0.47
Quality 1, 2, and 3 (no.)	4.9 ± 1.6	5.6 ± 0.8	4.1 ± 1.1	5.3 ± 1.4	0.49
Fertilized (%)	76.9 ± 7.1	77.0 ± 6.6	77.6 ± 7.6	78.4 ± 7.1	0.99
Degenerated (%)	35.2 ± 8.5^{a}	12.6 ± 4.6^{b}	14.5 ± 6.3^{b}	9.6 ± 3.7^{b}	0.02
Quality 1 and 2 (%)	38.0 ± 8.7^{a,b}	61.3 ± 8.2^{ab,A}	60.6 ± 9.4^{ab,A}	63.4 ± 8.6^{a,A}	0.14
Quality 1, 2, and 3 (%)	41.7 ± 8.8^{b,B}	64.4 ± 8.2^{ab,A}	63.1 ± 9.3^{ab,A}	68.9 ± 8.7^{a,A}	0.13
Degenerated of fertilized (%)	46.9 ± 9.6^{a,A}	17.4 ± 6.4^{b,B}	24.8 ± 9.3^{ab,A}	16.2 ± 7.0^{b,B}	0.04
Quality 1 and 2 of fertilized (%)	48.4 ± 9.5^{b}	78.3 ± 6.6^{a}	72.6 ± 9.5^{a}	77.7 ± 7.4^{a}	0.05
Quality 1, 2, and 3 of fertilized (%)	53.2 ± 9.6^{b,B}	82.6 ± 6.4^{a,A}	75.2 ± 9.3^{a,AB}	83.8 ± 7.0^{a,A}	0.04
Recovery rate (%)	45.6 ± 7.4	55.1 ± 6.9	35.4 ± 6.7	45.3 ± 5.8	0.25

^{a,b}Values within a row with different superscript lowercase letters differ at $P < 0.05$.
^{A,B}Values within a row with different superscript capital letters differ at $P < 0.15$.
[1]Fourth quartile = most BW (BW+) loss.

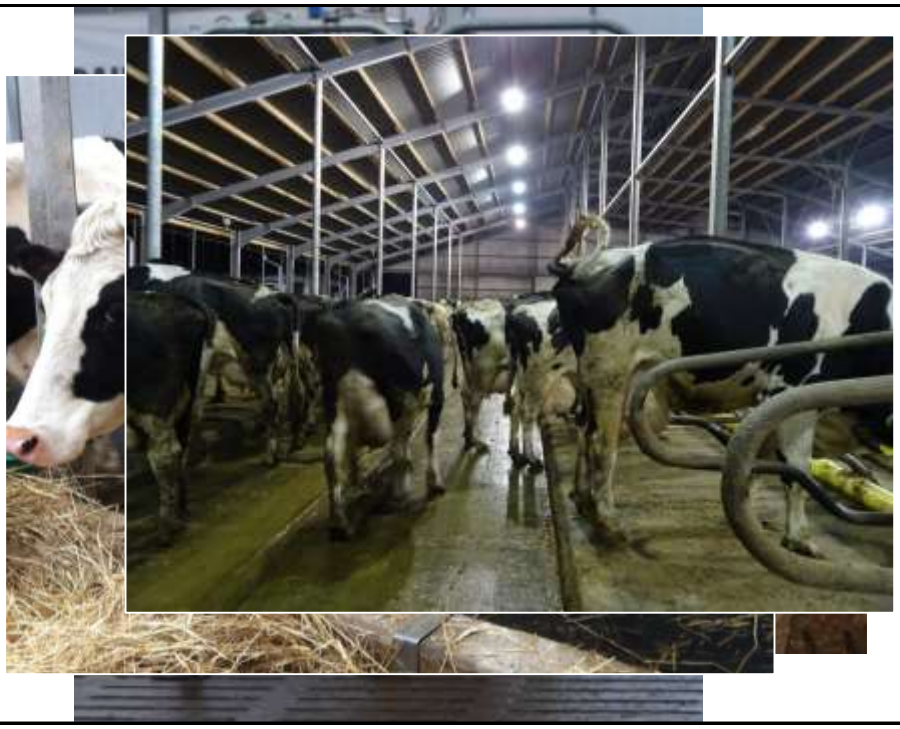
Carvalho et al., JDS 2014



Ribeiro et al. 2016

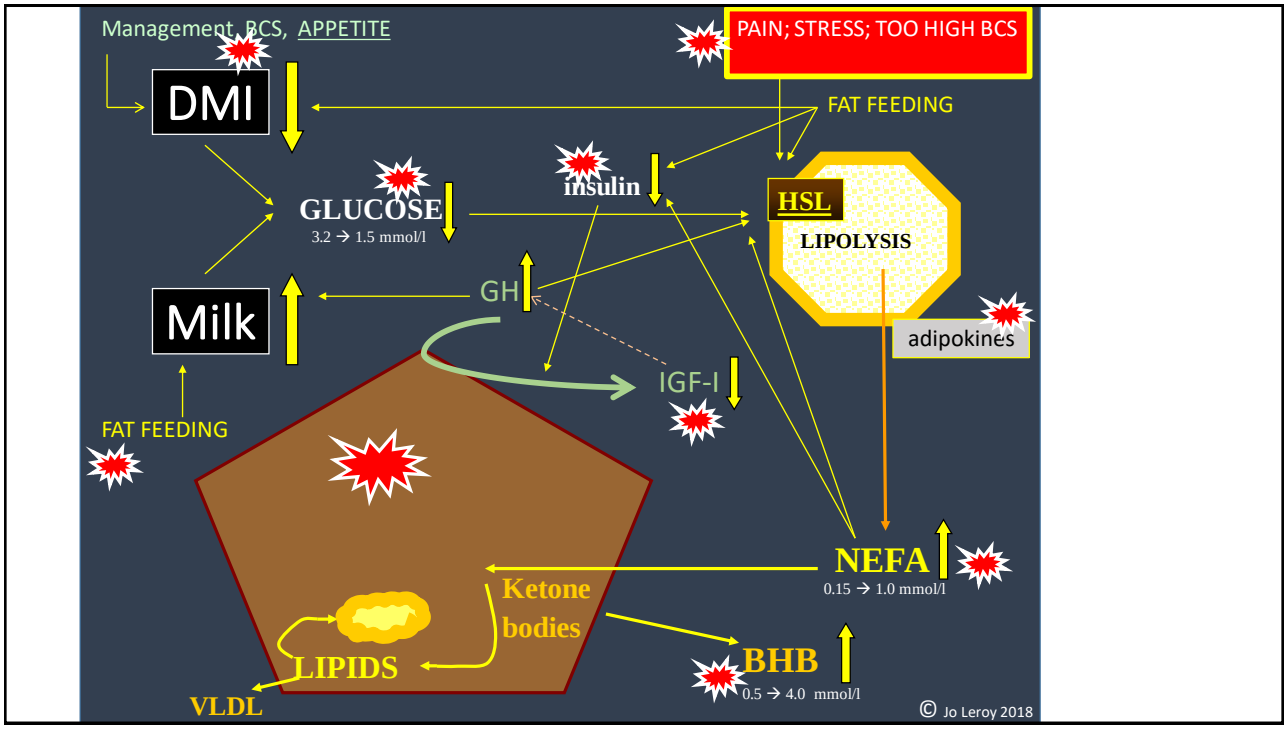
Upon ovulation, … the oocyte will remember this!

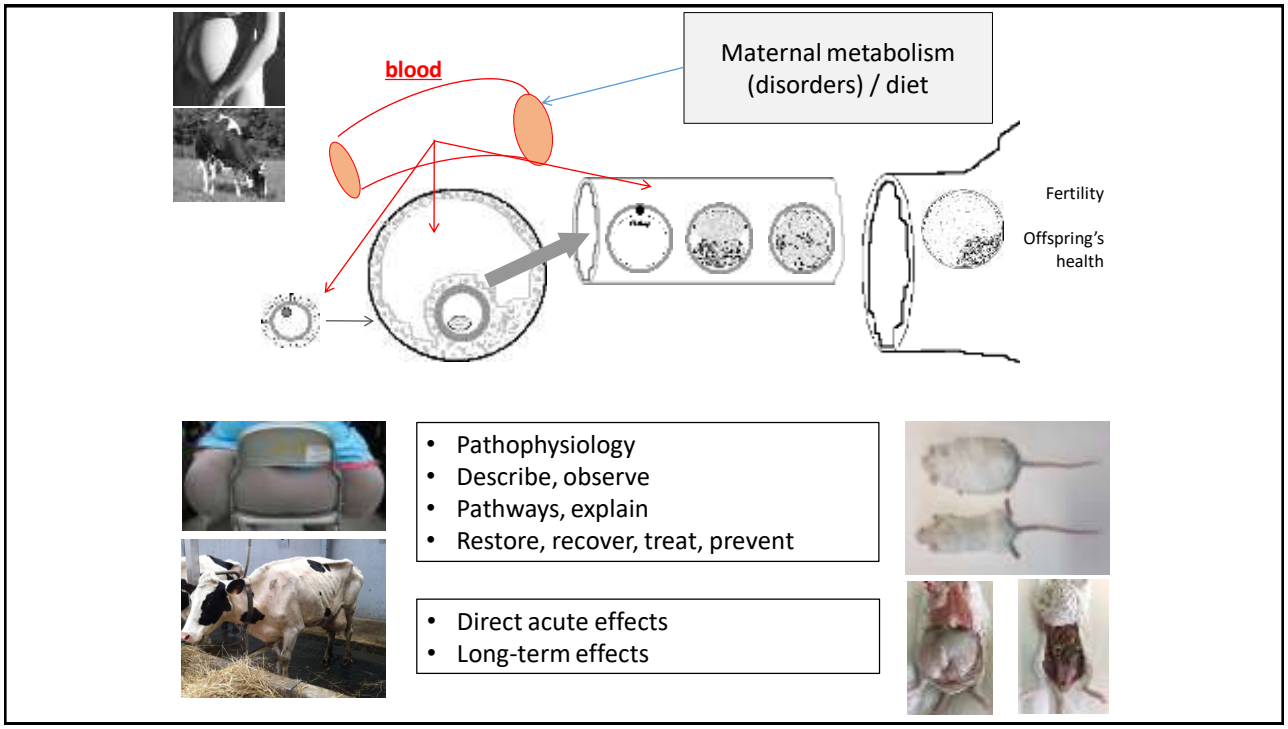
Ovsynch protocols never improve oocyte quality!



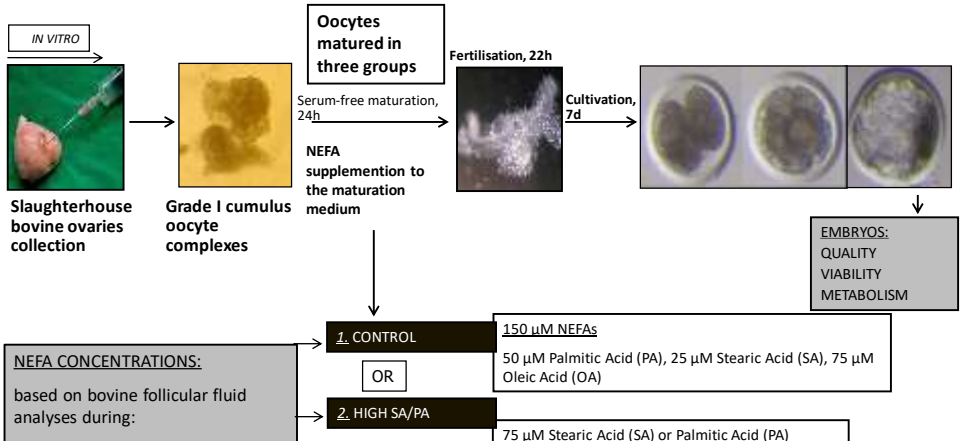
In this talk …

- Energy metabolism and fertility: focusing on what really matters
- Fertility … the deep dive
- How to set optimal metabolic health and fertility:
  - Go for a healthy cow!
  - CCP's for fertility … the real list!
  - Feeding for fertility? Yes, we can!
- Conclusions

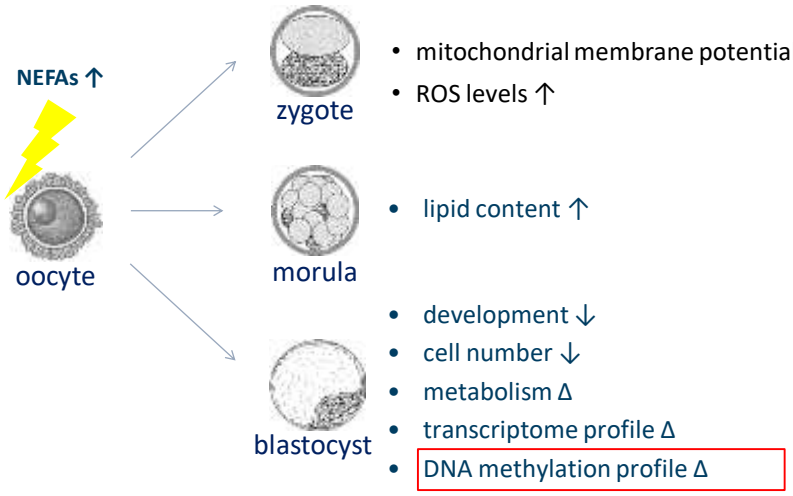

Management, BCS, APPETITE
DMI
PAIN; STRESS; TOO HIGH BCS
FAT FEEDING
GLUCOSE
3.2 → 1.5 mmol/l
insulin
HSL
LIPOLYSIS
Milk
GH
adipokines
IGF-I
FAT FEEDING
NEFA
0.15 → 1.0 mmol/l
Ketone bodies
LIPIDS
VLDL
BHB
0.5 → 4.0 mmol/l
© Jo Leroy 2018


blood
Maternal metabolism (disorders) / diet
Fertility
Offspring's health
• Pathophysiology
• Describe, observe
• Pathways, explain
• Restore, recover, treat, prevent
• Direct acute effects
• Long-term effects


17/06/2014

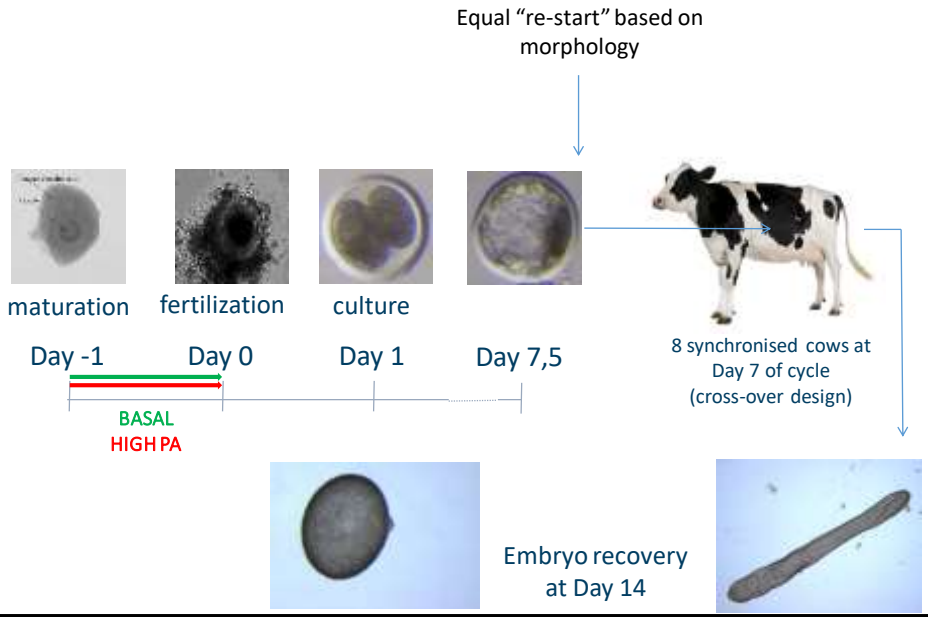

IN VITRO
Slaughterhouse bovine ovaries collection
Grade I cumulus oocyte complexes
Oocytes matured in three groups
Serum-free maturation, 24h
NEFA supplemention to the maturation medium
Fertilisation, 22h
Cultivation, 7d
EMBRYOS:
QUALITY
VIABILITY
METABOLISM
NEFA CONCENTRATIONS:
based on bovine follicular fluid analyses during:
→physiological conditions (1)
→NEB conditions (2 and 3)
(Leroy et al., 2005)
1. CONTROL
150 µM NEFAs
50 µM Palmitic Acid (PA), 25 µM Stearic Acid (SA), 75 µM Oleic Acid (OA)
OR
2. HIGH SA/PA
75 µM Stearic Acid (SA) or Palmitic Acid (PA)
OR
3. HIGH COMBI
425 µM NEFAs
150 µM Palmitic Acid (PA), 75 µM Stearic Acid (SA), 200 µM Oleic Acid (OA)

Lipotoxicity and oocyte quality

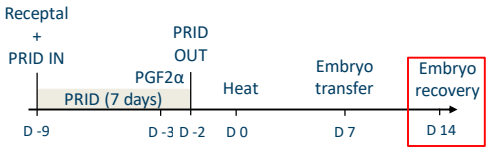


Leroy *et al.*, Animal Reproduction 2017
Desmet *et al.* BMC Genomics 2016

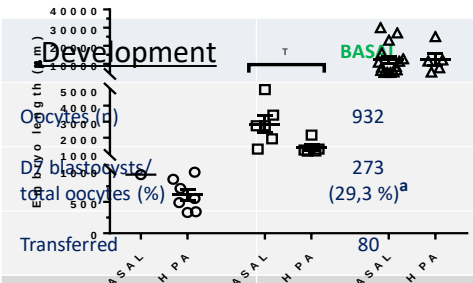
Experimental design embryo transfer



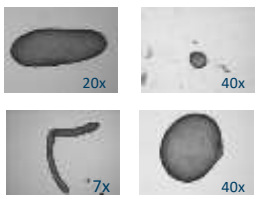
Embryo recovery

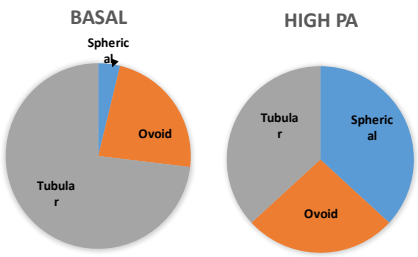


Development

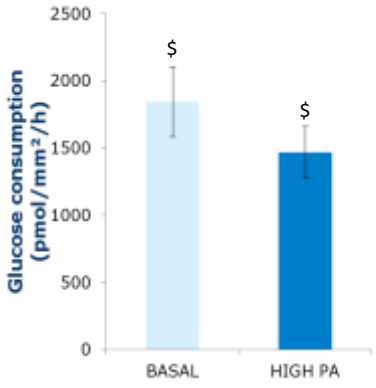


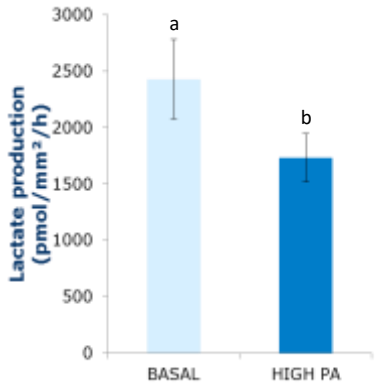
	BASAL	HIGH PA
Oocytes (n)	932	1062
D7 blastocysts/ total oocytes (%)	273 (29,3 %)[a]	262 (24,7 %)[b]
Transferred	80	80
D14 embryo recovery (%)	26 (32,5%)	19 (23,8%)



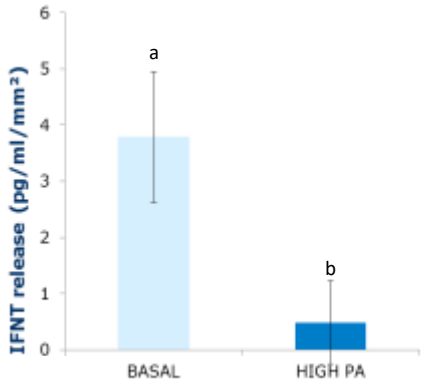


Metabolic profile





IFN_t release



Transcriptome profile

	ED			EXT		
	Morph.	Ovoid Male	Tubular Male	Morph.	Ovoid Male	Tubular Male
DEGs	13 ↑ 14 ↓	21 ↑ 38 ↓	11 ↑ 13 ↓	1 ↑ 1 ↓	4 ↑ 5 ↓	308 ↑ 333 ↓
Glucose metabolism	X					X
One-carbon metabolism	X					
Lipid metabolism		X		X		X
Tricarboxylic acid cycle						X
Insulin signaling						X
Redox-regulating mechanisms	X	X			X	X
ER stress induced apoptosis		X				
DNA repair	X					
Embryonic development						X
Cellular differentiation		X				
Epigenetic mechanisms						X
Protein synthesis			X		X	
Gene transcription and translation			X		X	
Molecular transport			X			
Immune response	X					

Conclusions from this study:

- Oocyte maturation in a lipotoxic micro-environment has long-lasting **carry-over effects** on post-hatching embryo development, cellular viability and transcriptomic profile despite good blastocyst formation at day 7 and transfer in a healthy uterine environment.
- Further trials are needed to translate this to humans.
- Data further highlight the importance of optimal maternal metabolic health around conception explaining pregnancy failure after successful day 7 embryo formation.

Bovine reproduction in HACCP terms

What are the CCP? Chronologically?

1. Puberty and heifer rearing
2. Calving
3. Uterine recovery
4. Onset o[illegible]
5. [illegible]ovulation
6. [illegible]semination and conception
7. Supporting early pregnancy

In a METABOLICALLY HEALTHY cow!

Feeding for fertility? Yes we can!

1) Feeding for optimal <u>liver health</u>
2) Feeding for <u>ovarian activity</u> (first weeks after calving)
   a. Optimizing Energy Balance and metabol[illegible]te, DMI, reducing BCS changes,)
   b. Fee[illegible] (starch) inducing high IGF-I and high glucose
   c. Som[illegible] dietary fats (saturated and omega-6)
   d. Some vitamines like Beta-carotene, Vit E, minerals, …
3) Feeding for optimal <u>oocyte and embryo quality</u> (at breeding).
   a. History of metabolic health
   b. Low insu[illegible] and high saturated fat)
   c. Low [illegible]ations
   d. Optimal protein/energy balance
   e. Anti-oxidants

Metabolic health

Oxidative stress

Measure first to manage after!

What is …

1) Metabolic health?
2) Energy balance?
3) Fertility?

What is “bad” fertility, energy balance or metabolic health? We need to define first before we try to alleviate!

Measuring Metabolic Health

- Monitor Dry matter intake
- Milk fat/protein ratio’s
- BCS changes over time
- Rumen fill, rumen pH
- Feces score
- Blood parameters: NEFA and BHB (before and after calving)

→Watch!
→Note and record!
→Keep it simple!
→Guarantee data quality!

Indicators for reproductive performance

- What is fertility?
- Value of the currently used indicators?
  - Calving interval
  - Non-return rates
  - Number of AI per pregnancy

→ Be warned!
- Informs only about management decisions
- Preference farmer
- "Confounded, biased, lag, momentum"
- Bad proxys for reproductive performances
- Bench-marking impossible!
- Very tricky to use as proxy to measure improvements after interventions

Reproductive performance

- Valid alternatives? (defined cohort, within a specific time interval, specific event):
  "what does the parameter tell you and what not: Management quality or intrinsic fertility (physiology)"
  - Heat detection rate (submission rate) (65/75%)
  - Conception rate (35/50%)
  - Pregnancy rate (20/26%)

  - % open cows at d120 pp (indicator for general health and well being)
  - % pregnant cows at d30 after the end of the VW period
  - % inseminated cows at d30 after the end of the VW period
  - Inter-oestrus (inter KI) interval
  - Cusum charts

In this talk …

- Energy metabolism and fertility: focusing on what really matters
- Fertility … the deep dive
- How to set optimal metabolic health and fertility:
  - Go for a healthy cow!
  - CCP's for fertility … the real list!
  - Feeding for fertility? Yes, we can!
- Conclusions

Conclusions

- Metabolic healthy cows will produce a lot of milk and will be fertile! However, …
- Modern dairy cows need our support
- The support should be:
  - Studied
  - Strategically designed to …
  - … result in measurable benifit
- Always put the metabolic health first!
- Never forget the oocyte's history!

MODERN Dairy cows NEED our SUPPORT: