Fertility/auglība – energy metabolism – insuline resistence (RQUICKI) - IGF1

a) genotype – 50%

b) **phenotype – 50% :**

- **Environment/vide** climate, housing
- **Feeding/ēdināšana**

Energy	**FFA, BHB**, bilirubine, cholesterol
Protein	urea, protein, albumin
Minerals	Na, K, Pi (Ca, Mg)
Acid-Base-Balance	alkalosis [K (NSBA)], (azidosis)
Trace elementes	Se, Cu, Zn, Co, Mn,
Vitamines	ß-Carotin, Vitamin A, - E, - C
Antioxidants	vitamins, trace elementes

Fertility – energy metabolism – insuline resistence (RQUICKI) - IGF1

Main focus:

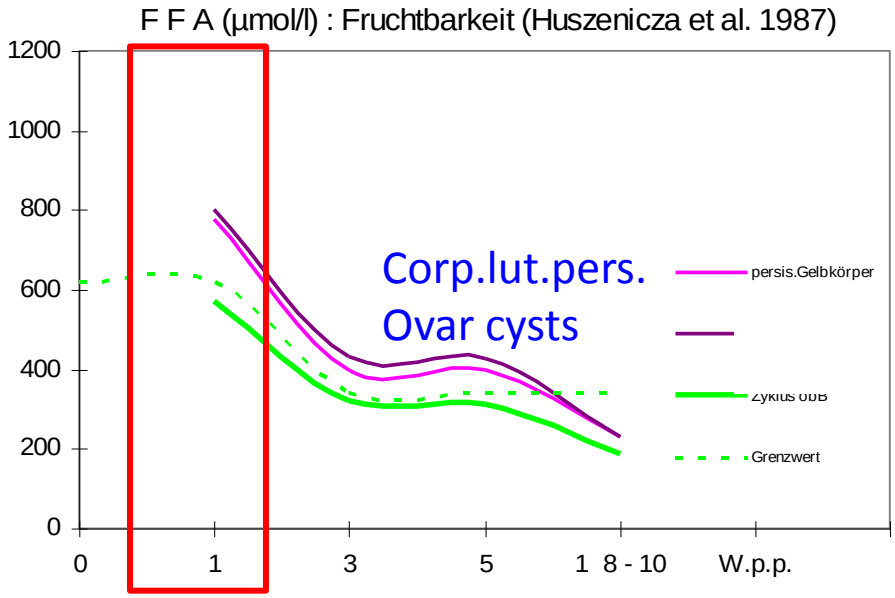
1. **F F A: after calving**

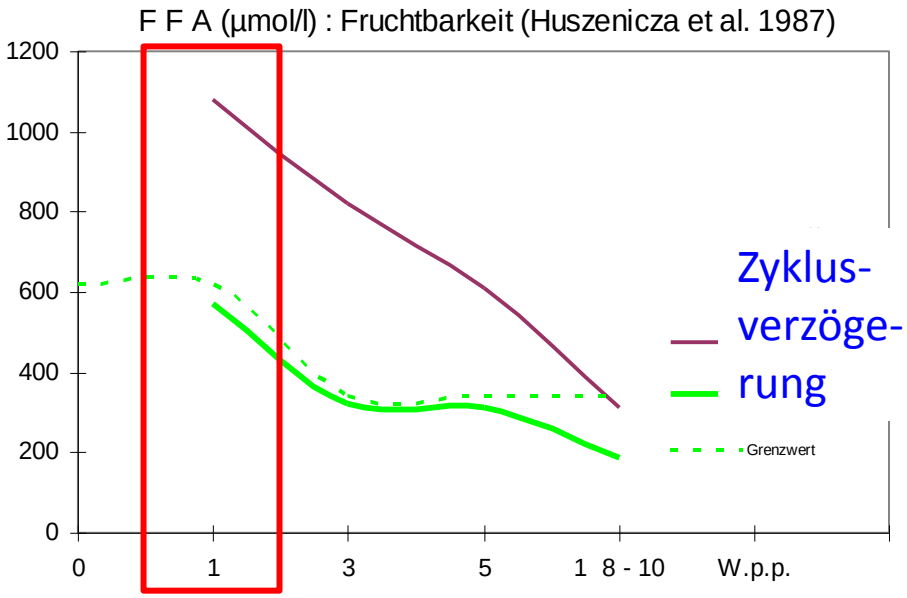
   during calving

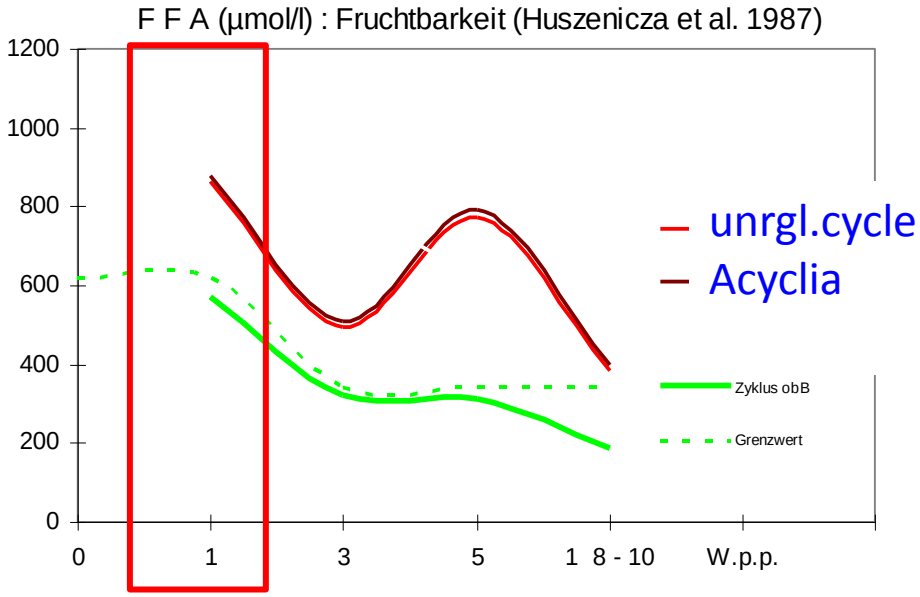
   before calving

2. F F A : days open
3. F F A : insuline resistence = RQUICKI
4. IGF_1

FFA after calving and ovar function







↑ Lipolysis : → ↑ Luteal phase
(Corp.lut.pers.)
oder *Lutein cysts*

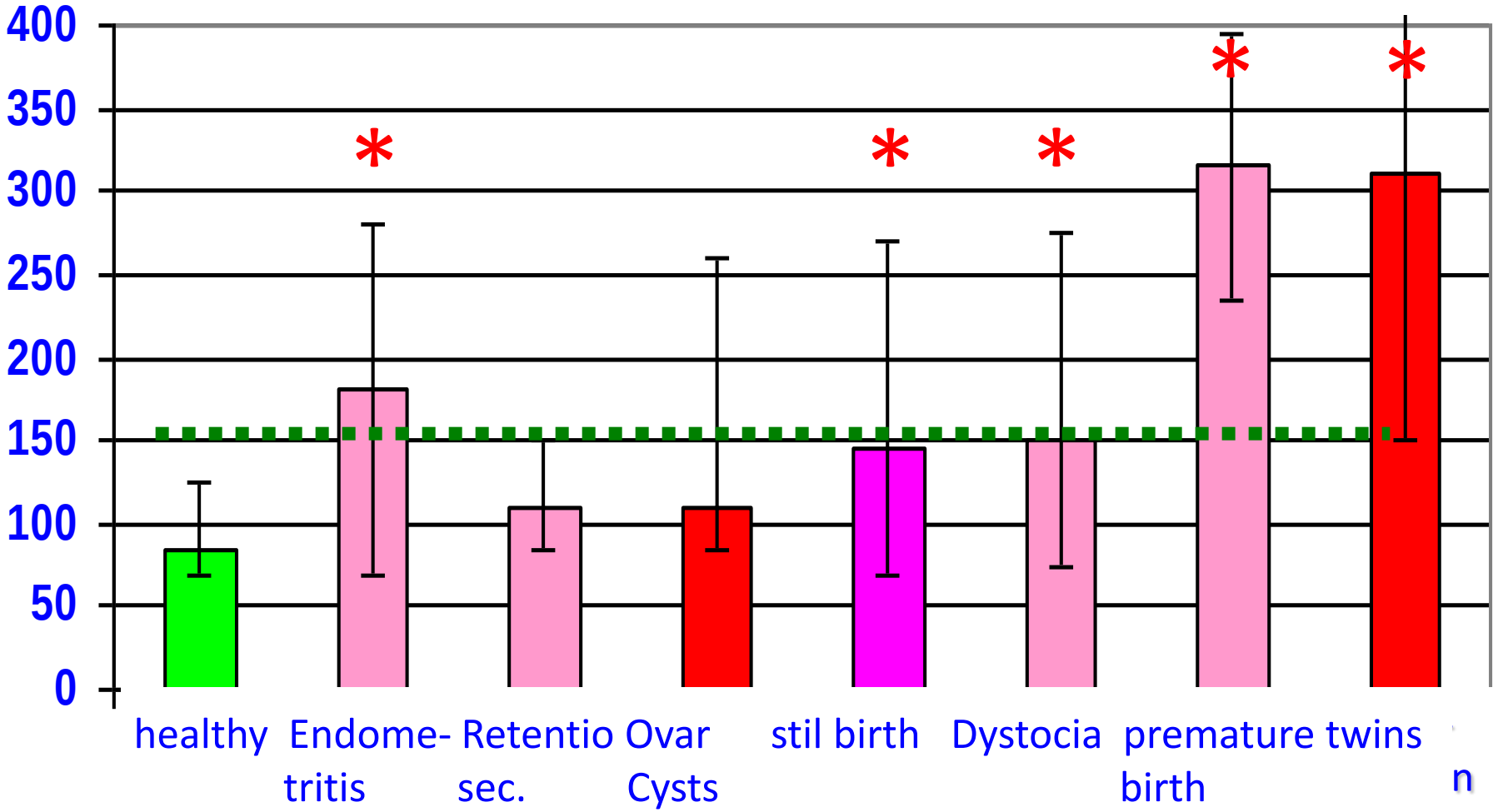
↑↑↑ Lipolysis :→ Azyklia or
Follikel cysts

Fertility – energy metabolism – insuline resistence (RQUICKI) - IGF1

Main focus:

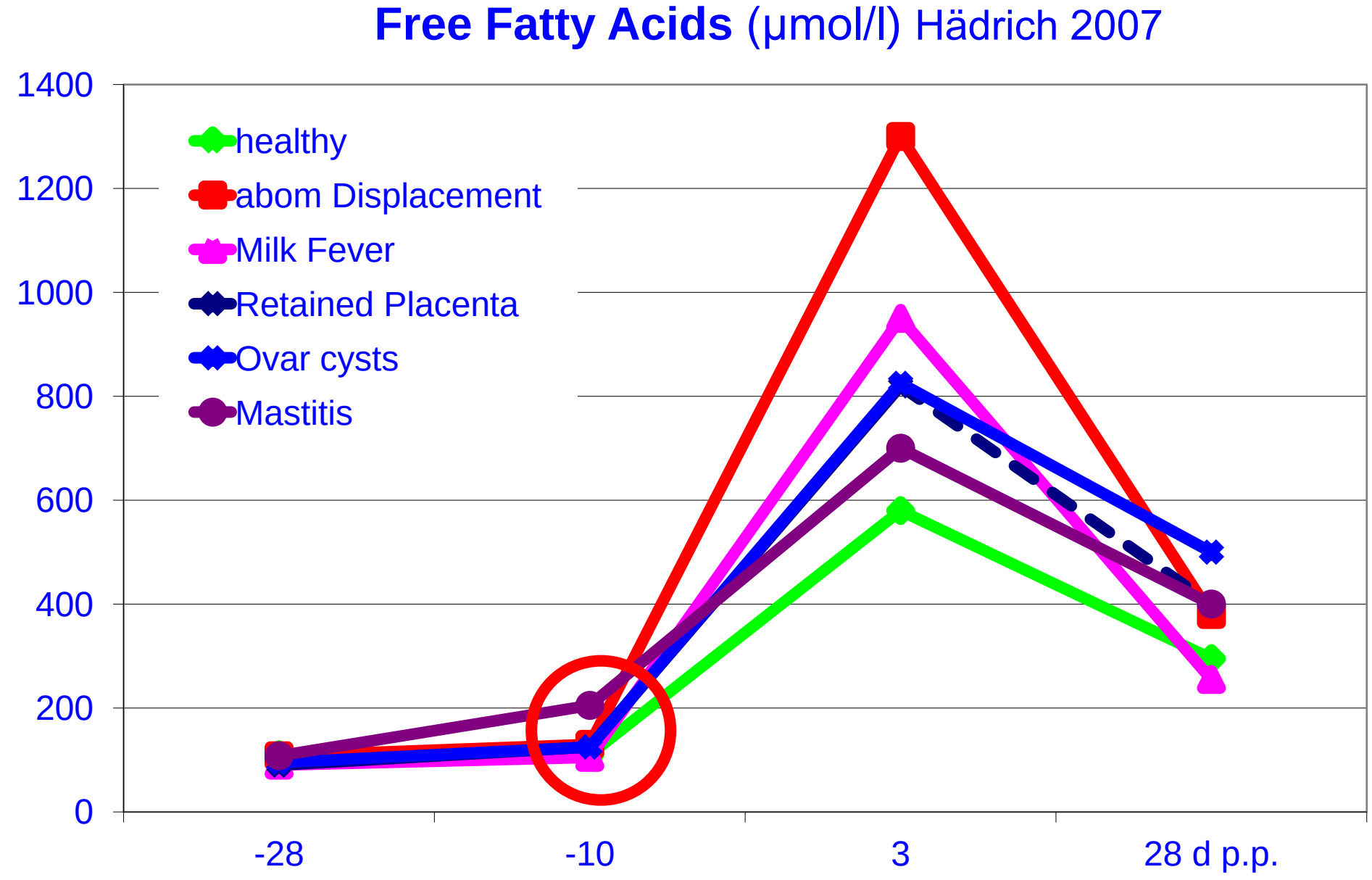
1. **F F A**: after calving
   during calving
   before calving
2. F F A : days open
3. F F A : insuline resistence = RQUICKI
4. IGF_1

Free fatty acids (µmol/l): 10 d **a.p.**



p<0,05 = *

Fürll et al. 2005


Free Fatty Acids (µmol/l) Hädrich 2007
1400
1200
1000
800
600
400
200
0
healthy
abom Displacement
Milk Fever
Retained Placenta
Ovar cysts
Mastitis
-28
-10
3
28 d p.p.

Fertility – energy metabolism – insuline resistence (RQUICKI) - IGF1

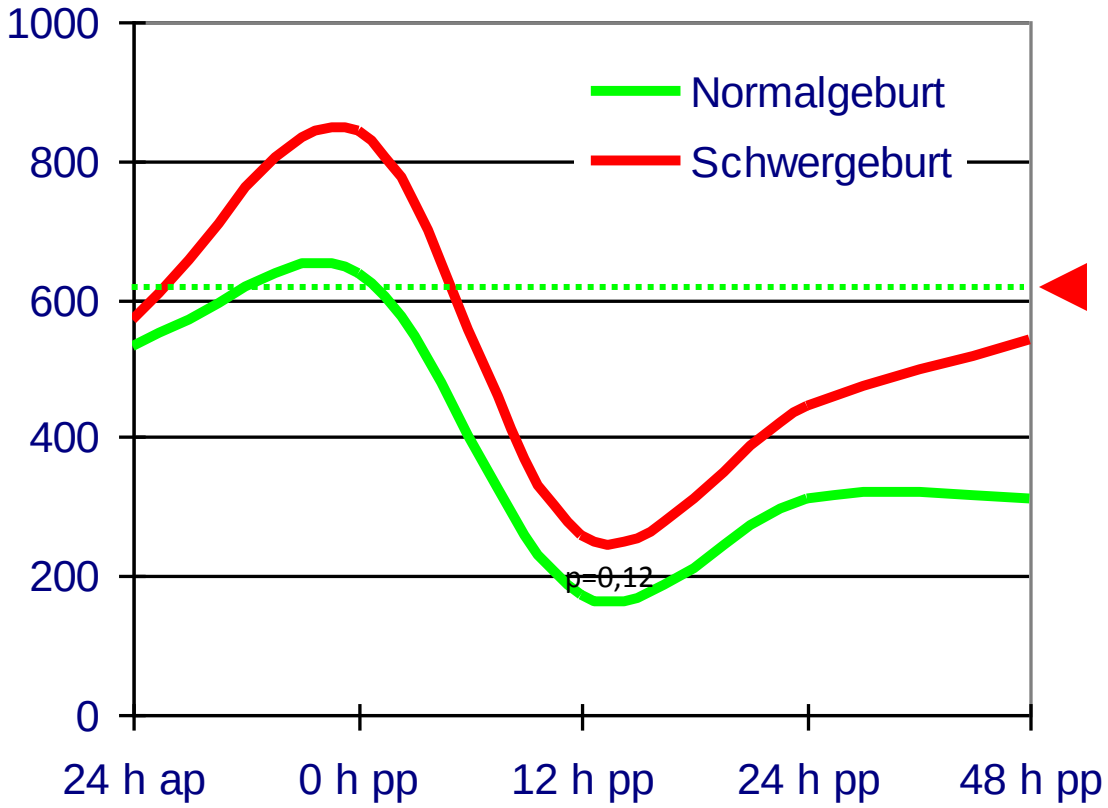
Main focus:

1. **F F A:** after calving

   during calving

   before calving
2. F F A : days open
3. F F A : insuline resistence = RQUICKI
4. IGF_1

F F A during calving (µmol/l)



Dystocia:

- ↑ during delivery

= ↑ **Lipolysis**

- permanent high↔ diseases

Relation to AO

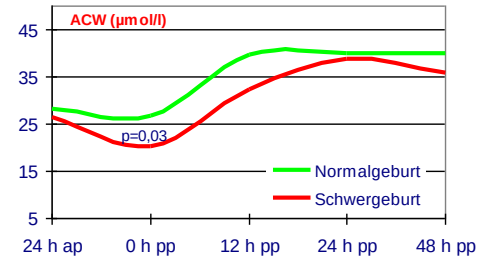
- neg. correlations to TEAC

- pos. to SOD, Albumin, Bilirubin

= ↑ **AO-loading,**

↑ **wastage**

	SOD	GPX	TEAC	GPX	TEAC	Albumin	Bilirubin
FFS r:	-	-	-	0,22	-	**0,30**	**0,68**
	0,28	**-0,28**	**-0,31**	-0,28	**-0,31**	**0,25**	**0,66**



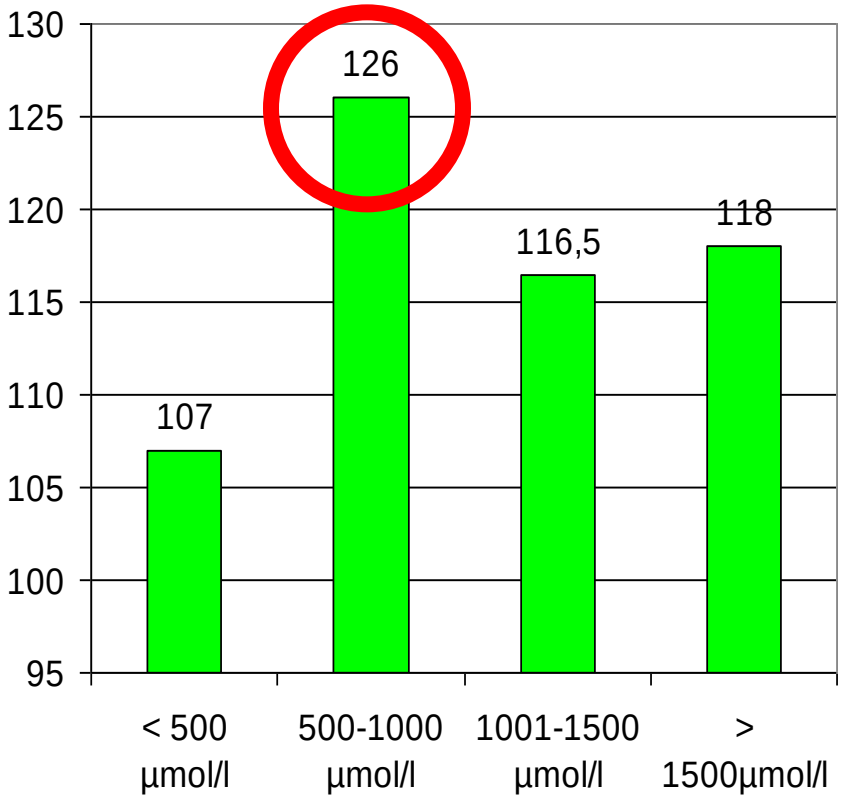
Fertility – energy metabolism – insuline resistence (RQUICKI) - IGF1

Main focus:

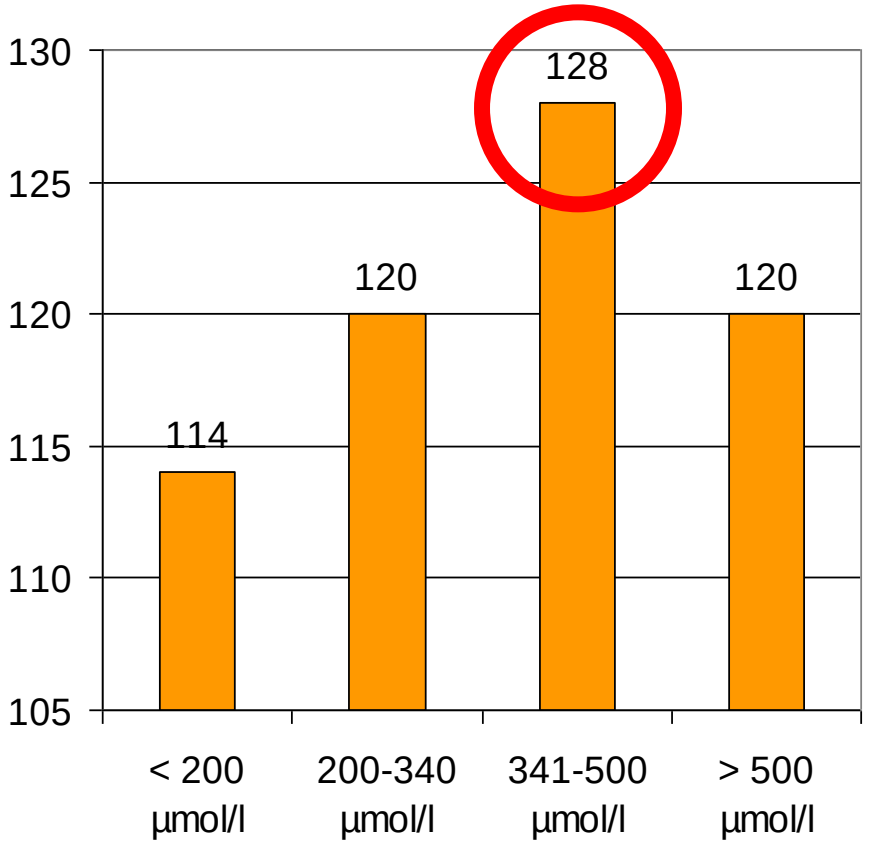
1. F F A: after calving
   during calving
   before calving
2. **F F A : days open**
3. F F A : insuline resistence = RQUICKI
4. IGF_1

F F A and days open

FFA class 3 d p.p. : days open



FFA class 28 d p.p. : days open



< 620 µmol/l

< 340 µmol/l

limit values

Fertility – energy metabolism – insuline resistence (RQUICKI) - IGF1

Main focus:

1. F F A: after calving
   during calving
   before calving
2. F F A : days open
3. **F F A : insuline resistence = RQUICKI**
4. IGF_1

Insuline resistence

- abnormal insulin **receptors**
- ↓**number** of receptors, - permanently elevated insulin levels
- **IgG antibodies** which inhibit the biological activity of the insulin
- ↑ **enzymatic cleavage** of insulin
- ↓ **binding** of insulin to its receptors
- **Insulin resistance-promoting proteins**: **TNF-alpha**, PAI-1 and resistin

Insuline resistence

- **Insulin resistance-promoting proteins**:

  TNF-alpha, PAI-1 and resistin

→ ↑ Glucose
→ ↑ FFA
→ ↑ insuline

$$\frac{1}{\lg \text{glucose} + \lg \text{FFA} + \lg \text{insuline}}$$

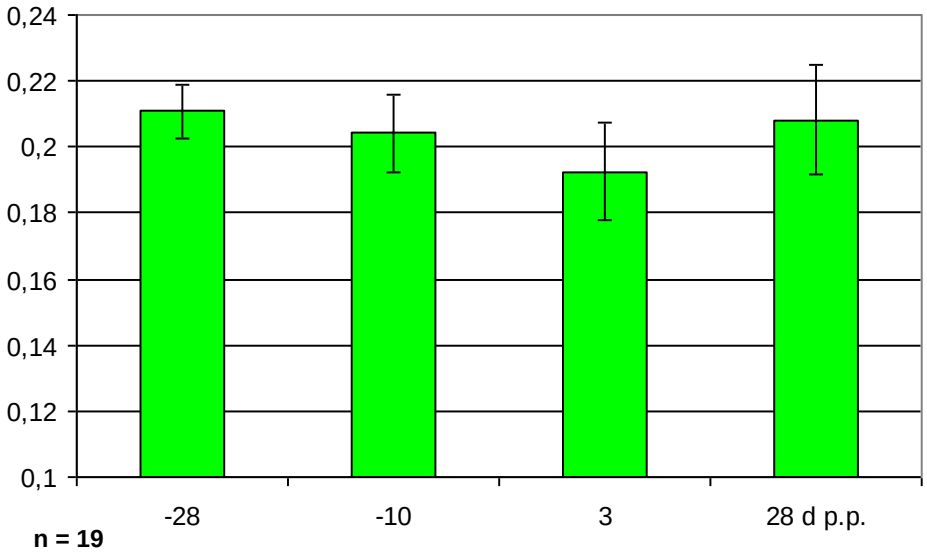
Revised Quantitative Insulin Sensitivity Check Index"

(RQUICKI)

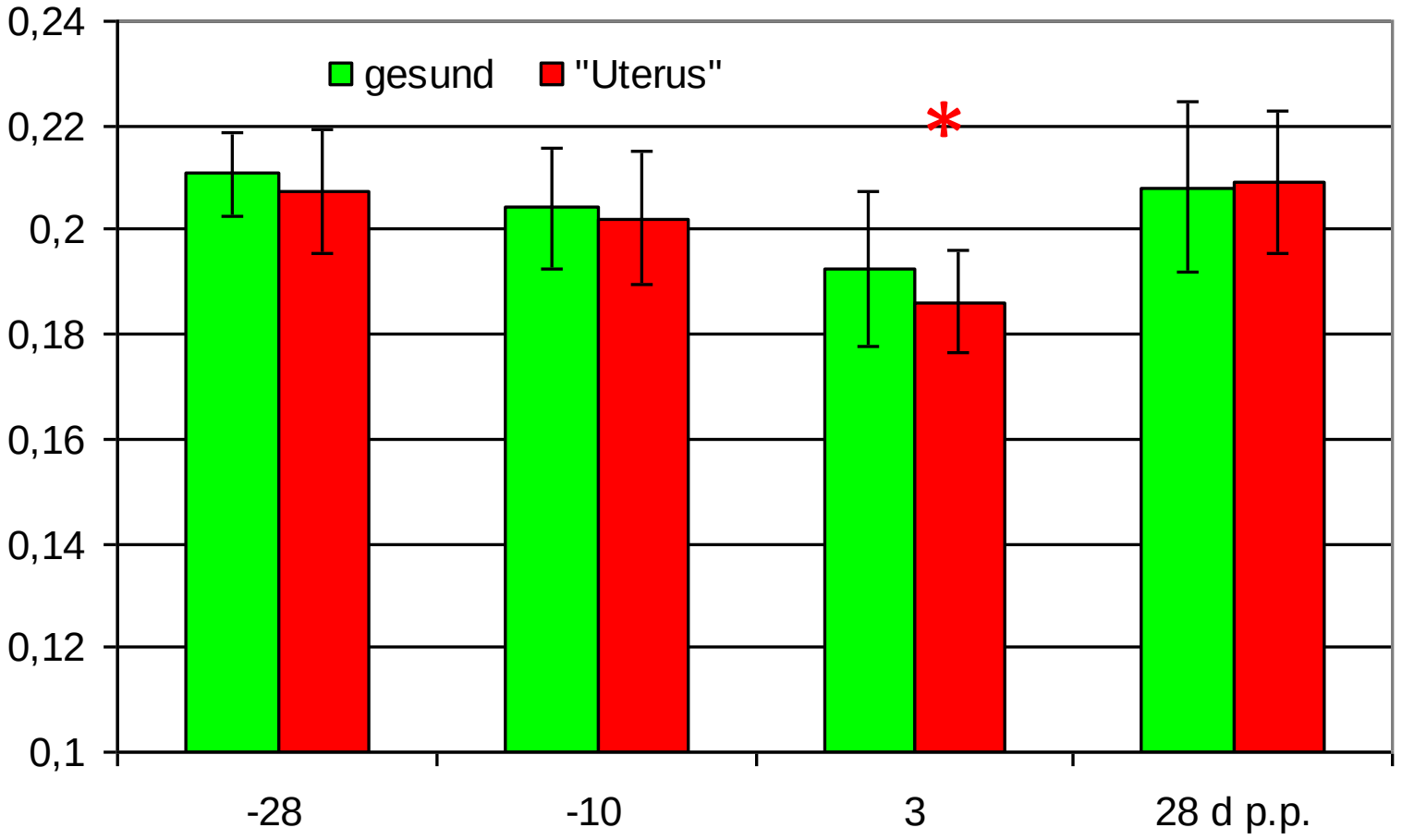
$$\frac{1}{\lg \text{Glucose} + \lg \text{FFS} + \lg \text{Insulin}}$$

0,18 – 0,22

„Insulinresistenz“ peripartal (RQUICKI mod.): **gesunde Kühe**

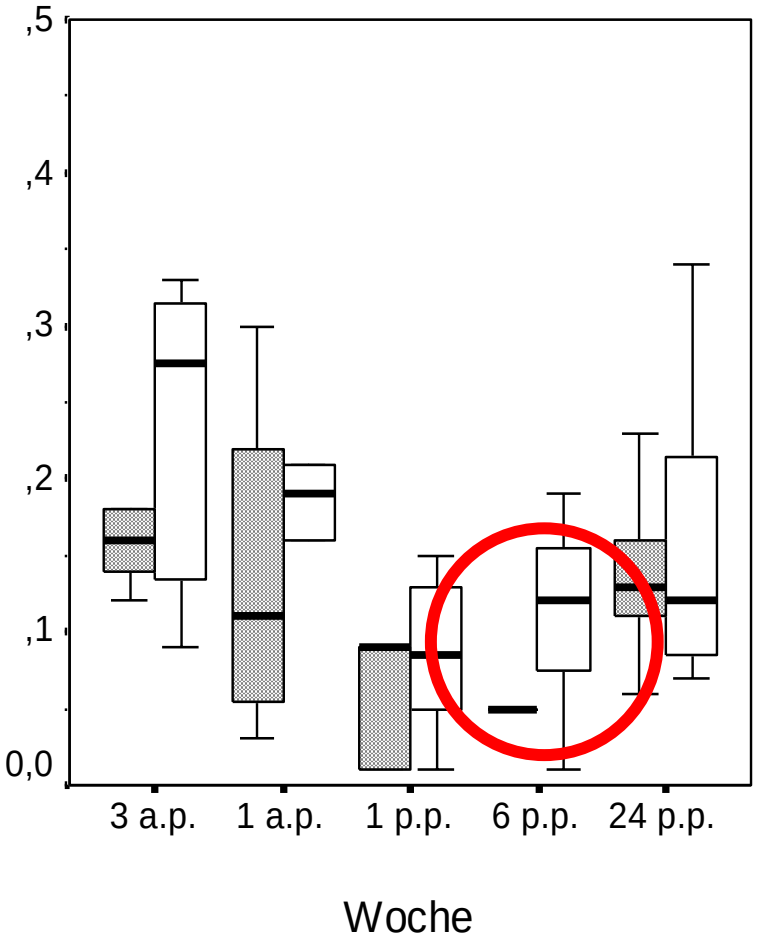


Revised Quantitative Insulin Sensitivity Check Index" healthy : uterus ill cows

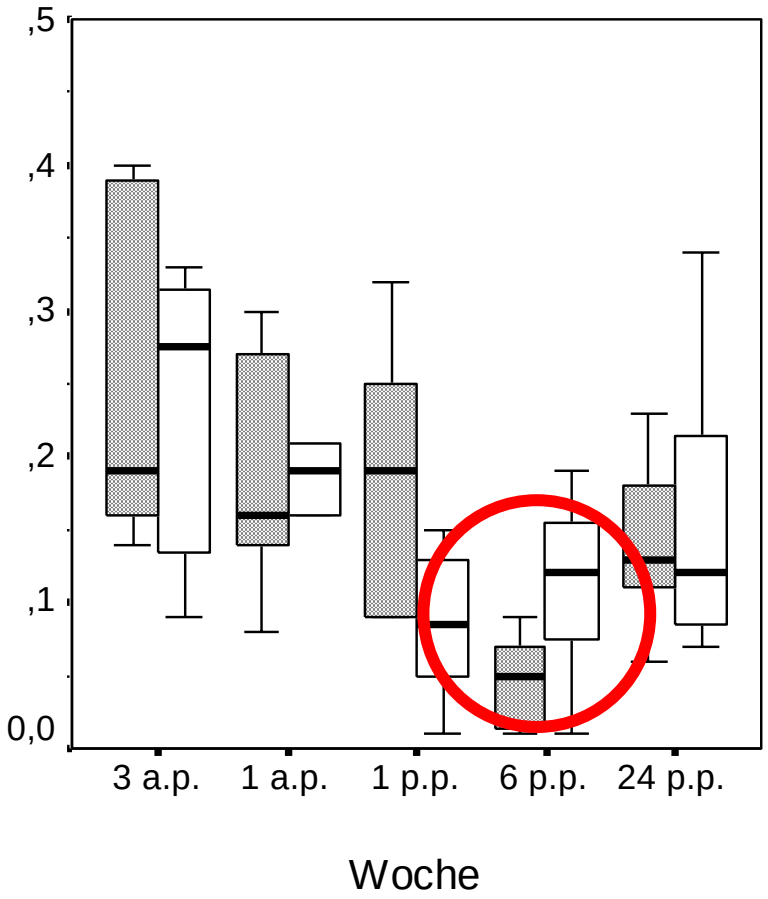


uterus ill: Fiever, Ret. sec., Endometritis/Lochiometra, Ovar cysts, twins *= p < 0,05

Insuline in healthy and cows with Ret. sec. and Ovar cysts (healthy= white)



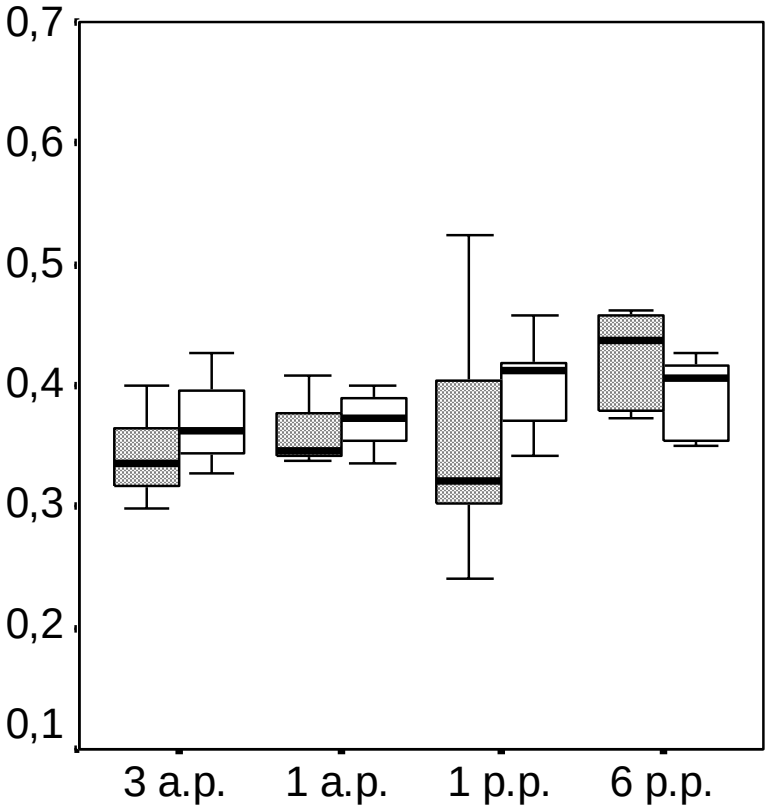
Ret. sec. : healthy

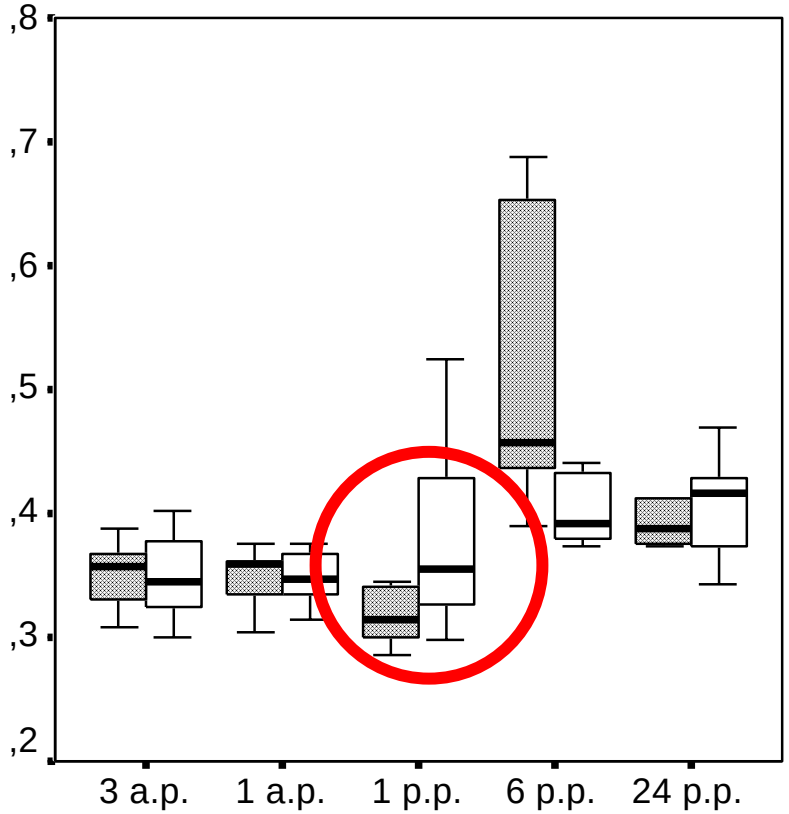


Ovar cysts: healthy

RQUICKI in healthy and cows with Ovar cysts

(healthy= white)





1. lactation : > 1 lactation

Ovar cysts: healthy

Fertility – energy metabolism – insuline resistence (RQUICKI

Σ: Free fatty acids

- Level and duration of lipolysis p.p. ≈ ovar disorders
- ↑ lipolysis already a.p. → fertility problems
- Dystocia → ↑ FFA and ↓ Anitioxidants
- fertility disorders = insulin resistance in 1th wk p.p.
- ↑FFA at 1th and 4th wk p.p. → longer days open
- tendency: ↑ FFA at 1th wk p.p. → ↓ productive live

FFA:

- most informative parameter

- best control = – 4 days p.p.
- different normal values a.p. – p.p.

↔ ad hoc therapy

↔ prophylaxis

NEUER Blut-Schnelltest – Calzium, Magnesium, Laktat und NEFA

a. **Calcium**
b. **Magnesium**
c. **L-Laktat**
d. **NEFA**

digitales Photometer

i. Calcium 1 Euro
ii. Magnesiuim 1 Euro
iii. Laktat 1,60 Euro
iv. NEFA 3,80 Euro

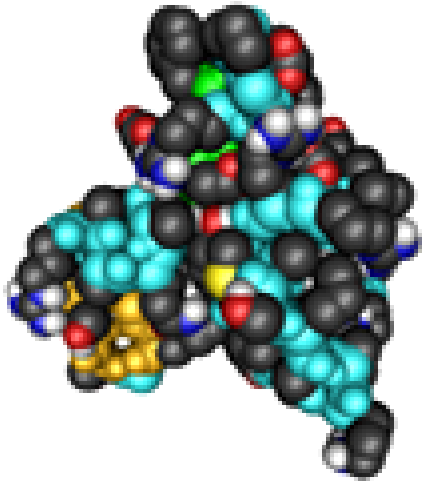
Idee

Clevere Produkte für erfolgreiche Tierhalter und Tierärzte

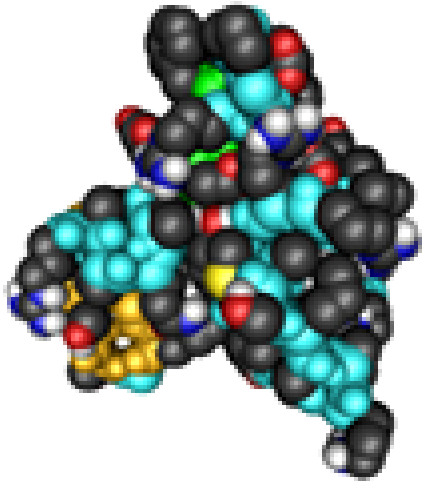
QUIDEE GmbH

IGF1

?

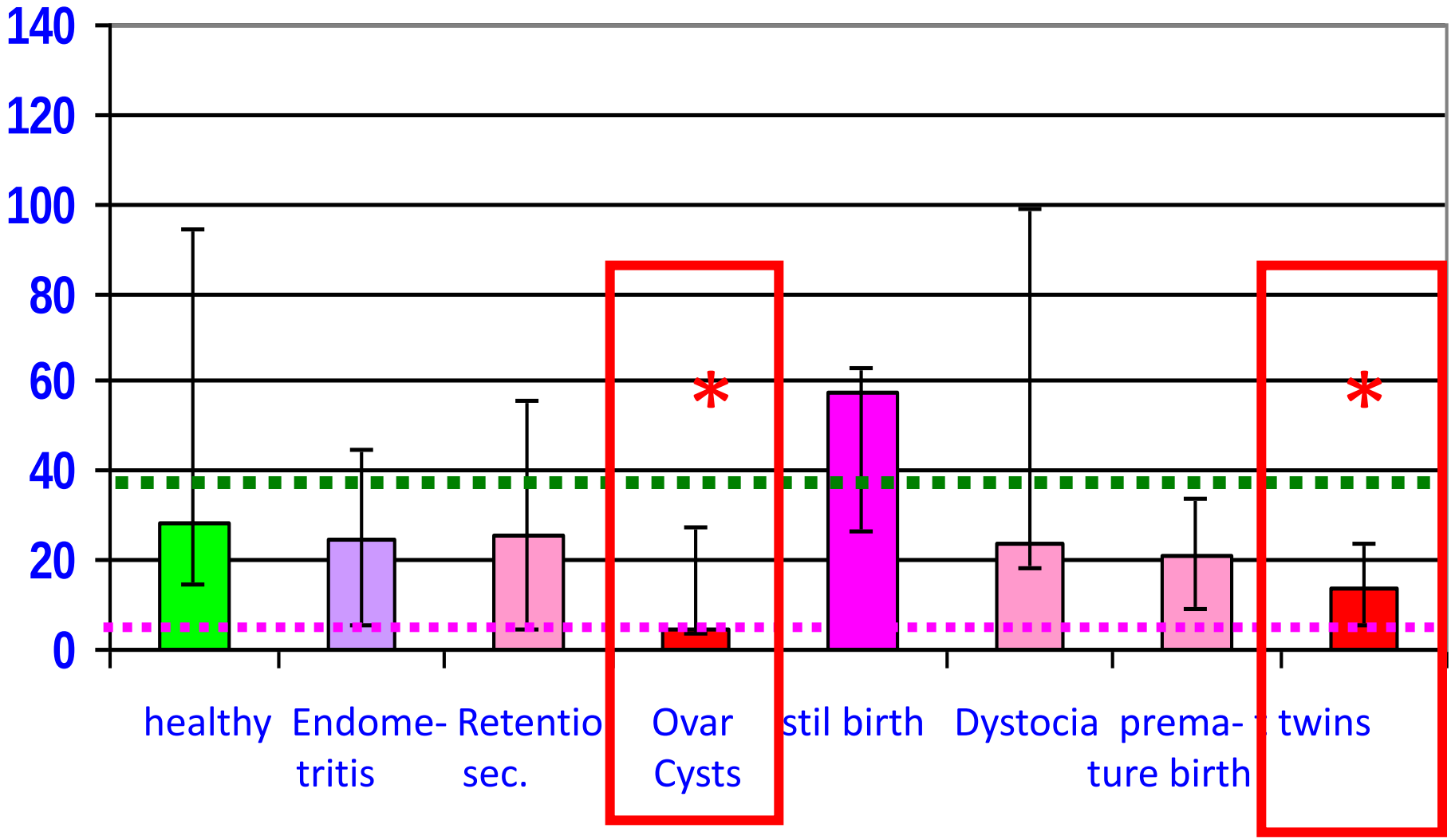


IGF_1 (Insulin-like growth factor-1)



- Stimulator of cell growth and proliferation
- Inhibitor of programmed cell death
- Synthesis in the liver
- indicator of the power supply
- key role in the follicular maturation and ovulation

IGF1 (ng/ml): 10 d a.p.

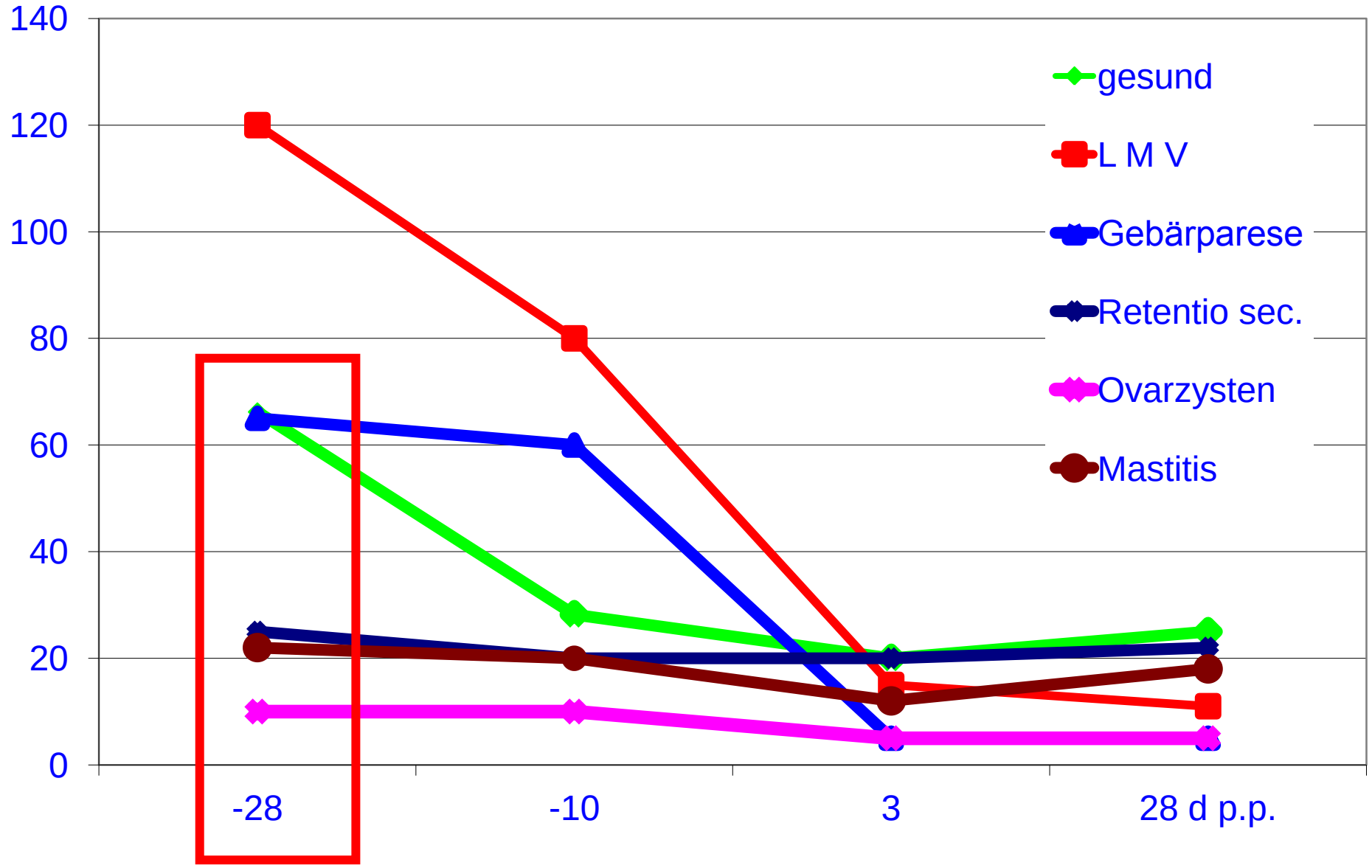


p<0,05 = *

IGF = Insulinähnlicher Wachstumsfaktor

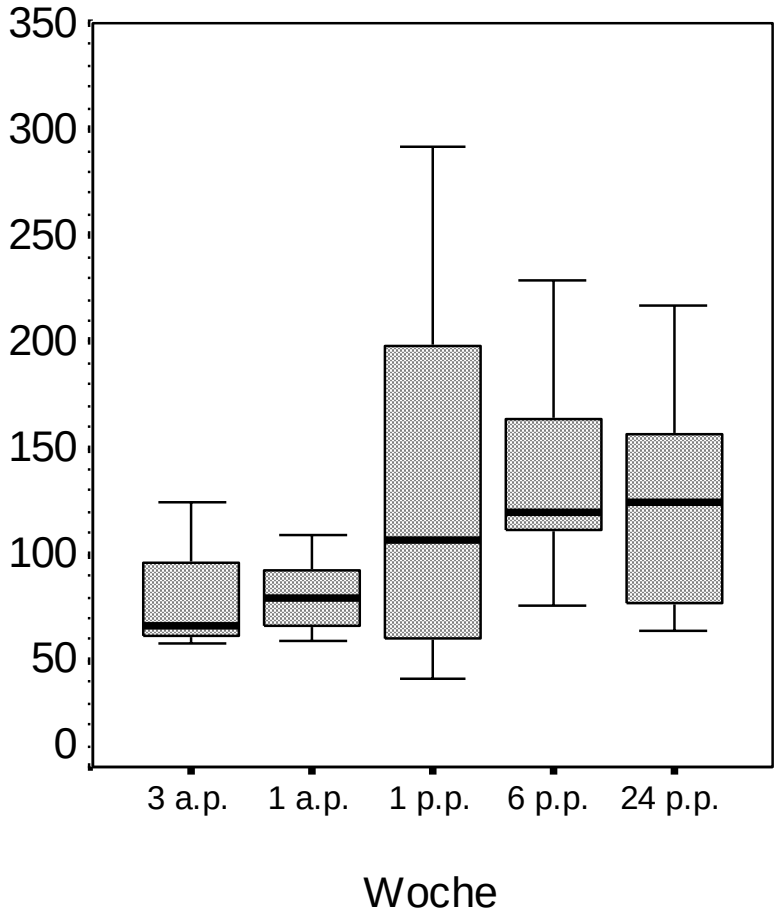
(Fürll et al. 2005)

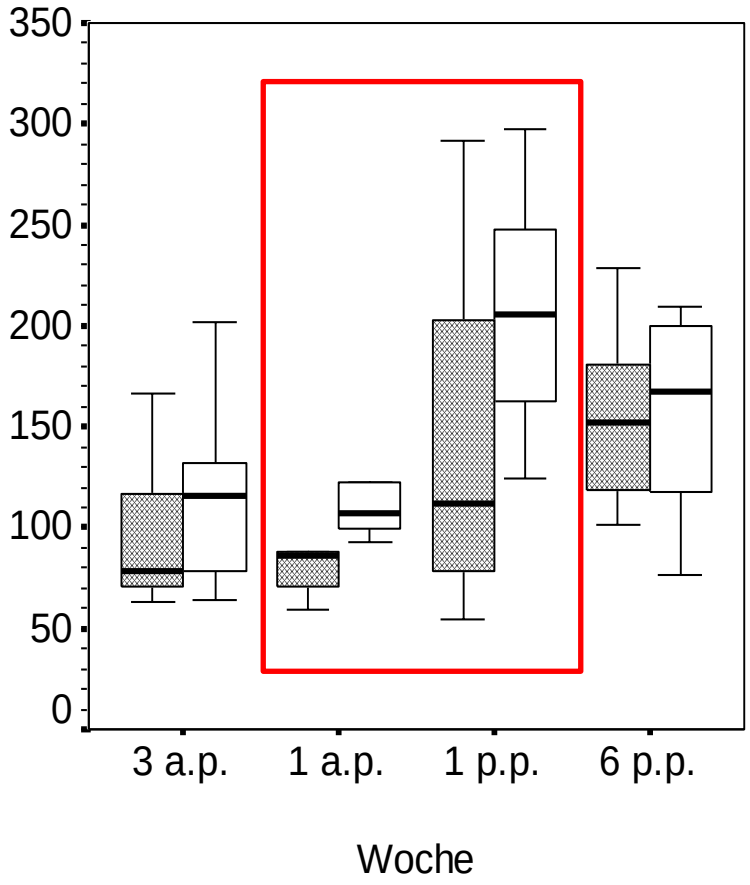
IGF1 (ng/ml) – Hädrich 2007



IGF1 peripartal 1. : > lactation

(Söllner-Donath 2013)



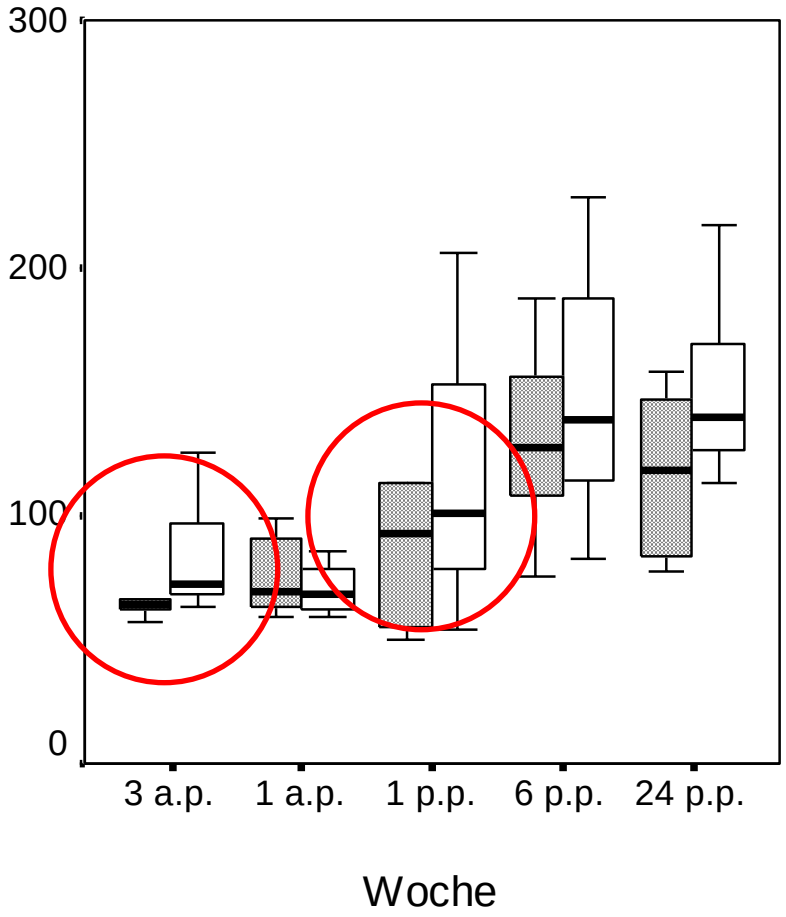


1. lactation

> 1 Lactation

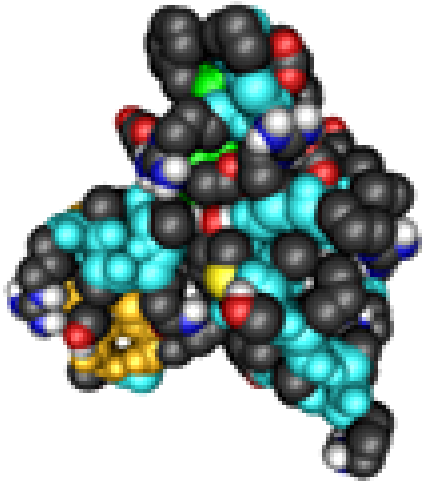
IGF1 in healthy and cows with Ovar cysts

(healthy= withe)



Ovar cysts: healthy

IGF1:



. . . early indicator -

already 4 weeks a.p. . .

.

Metabolic-Screening-Fertility

Problem	control weeks			Labor parameter in blood or other substrances
	1 a.p.	1 p.p.	3-8 p.p.	
Energy	X	**X**	X	**FFS, BHB**, Cholesterol, Bilirubin
Protein		**X**	X	**Harnstoff,** Protein (Albumin)
Liver metabolism	X	**X**	X	GLDH, GGT: B
Uterus	X	**X**	X	**CK,** AST**: B**
ABB	X		X	**K, NSBA, pH-Wert,** Pi, Ca: H
Minerals	X	**X**	X	Ca: B, H; **Pi.: B, H**
	X		X	**Na, K: H**
Trace elements			X	J: B, Ha; **Mn: Voll-B,Ha**,AP: B **Cu: B, Ha**; Zn: Ha; **Se: B,** GPX: Voll-B
ß-Carotin			X	**ß-Carotin (B, L)**
Vitamin E, -C, -A			X	Vitamin E, -C, -A (Vit. A B, L)
Antioxidants			X	TEAC,(ACW, ACL)

Health stabilization – „ad hoc“by the veterinarian

Conc. energy substances	Propylene glycole et al
lipolysis inhibition	„Energy“ (drinking trough, Drench, parenteral) Vitamin B12 (Catosal®, TIRASANA®) „Dexamethason“
digestive aids	Genabil®
intestinal stabilization	Dystikum®
Antioxidants	Vitamin E/ Selen, Cu, Mn, Se, u.a. ß-Carotin
Calciumhomöostasis	DCAD, Ca-Salts oral, Vitamin-D_3

Mastitis accumulation - are not enough antioxidants to blame?

M. Fürll, Medizinische Tierklinik, Leipzig

http://www.que.at/html/nutztiere/rind/mastitis.html

Mastitis

- cause for selection before fertility disorders and claw diseases
- 2-4 cents per liter of milk → ca. 150-200 € / cow / year
- by subclinical mastitis = damage 20-50 times more likely

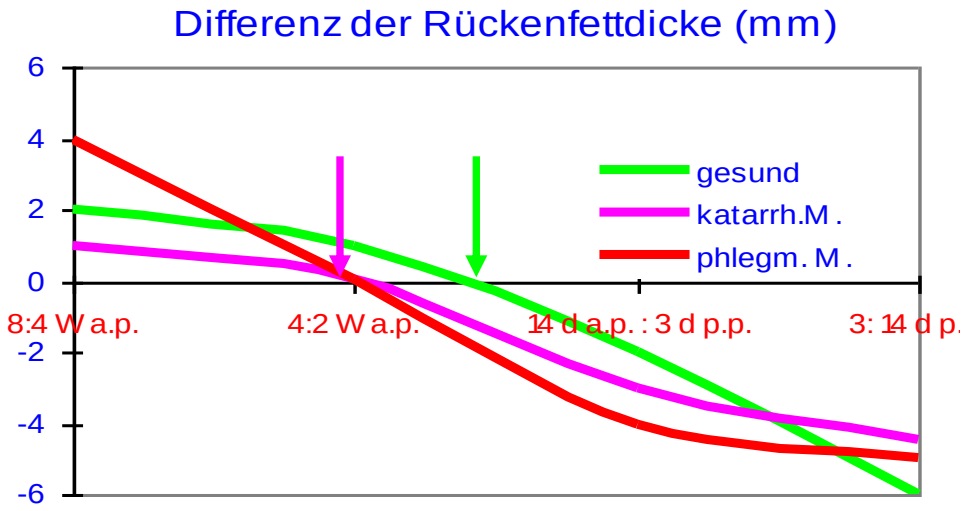
↓

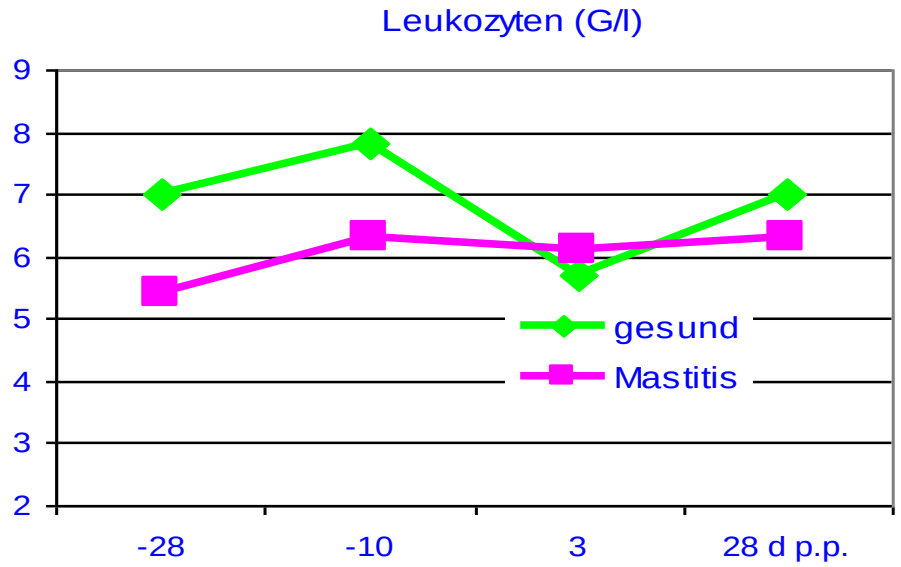
Importance for economics and animal welfare ↑

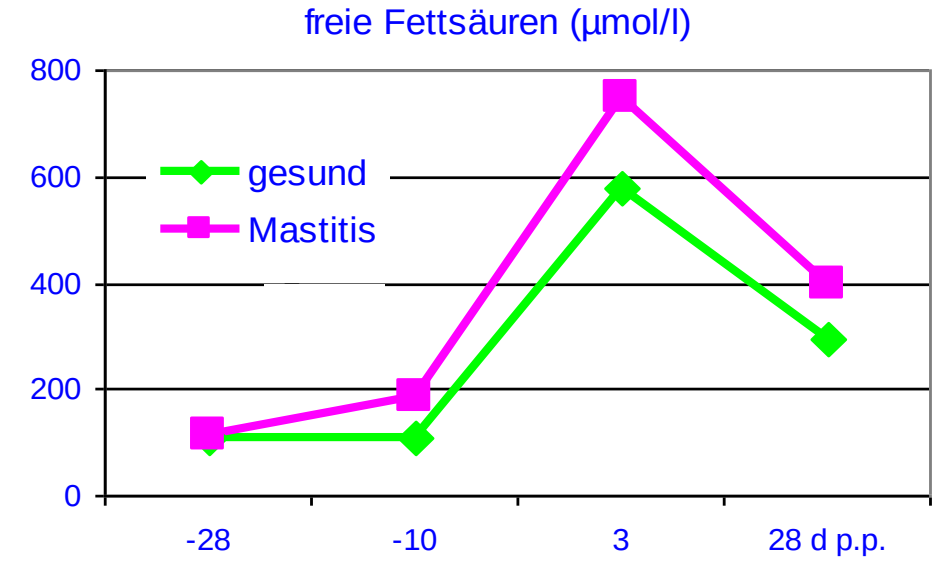
Feeding loads and udder health (Wendt et al. 1998)

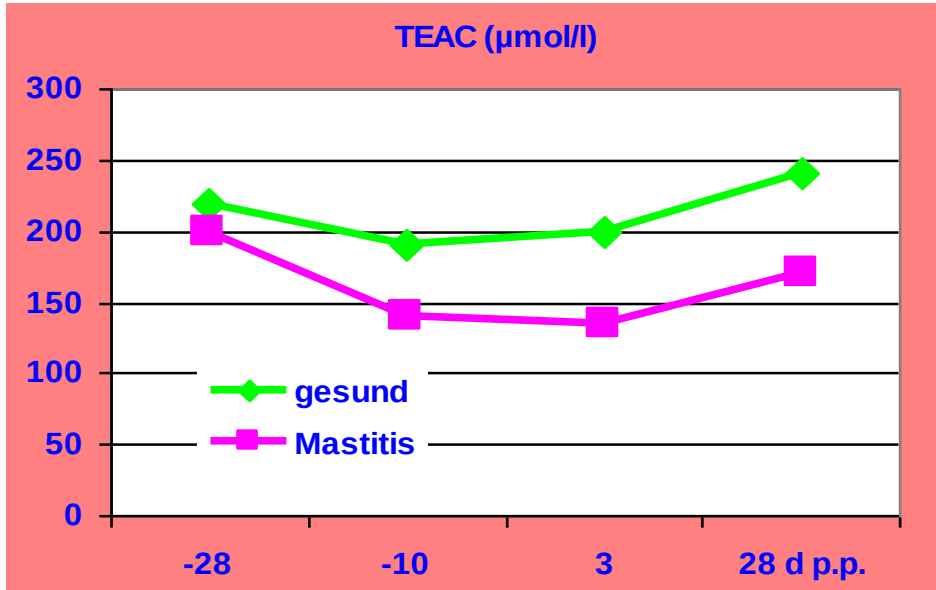
Factor	effects	follow
* ↓ **Energy** post partum **Ketosis** – subklinisch - klinisch	„liver damages“ ↓ **Phagozytosis** **Immunsuppression**	Mastitis ↑ cell count ↑ Fat
* ↑ **Protein**	↑ NH3/rumen Liver stress	subcl. Mastitis clin. Mastitis
* ↑ **carbohydrates** ↓ **crude fiber**	**Rumen azidosis** ↓ Ca	↑ cell count clin. Mastitis
* **Phytöstrogens** **Mykotoxins**	Östrogen effects **Immunsuppression** ↓ **Phagozytosis**	edema ↑ cell count Mastitis
* **Nitrat/Nitrit** **manure-N** **Brassica-feeding**	Immunsuppression Hypoxämia, mucous membrane irritation	↑ cell count, Vitamin demand, mucous membrane irritation
* ↓ **ß-Carotin** ↓ **Vitamin E/Se**	**Immunsuppression** ↓ **Antioxidants**	subkli. Mastitis latent infections

Early diagnosis of **Mastitis**



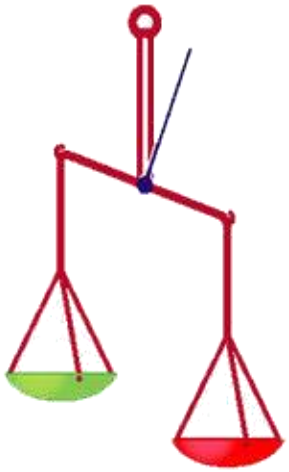






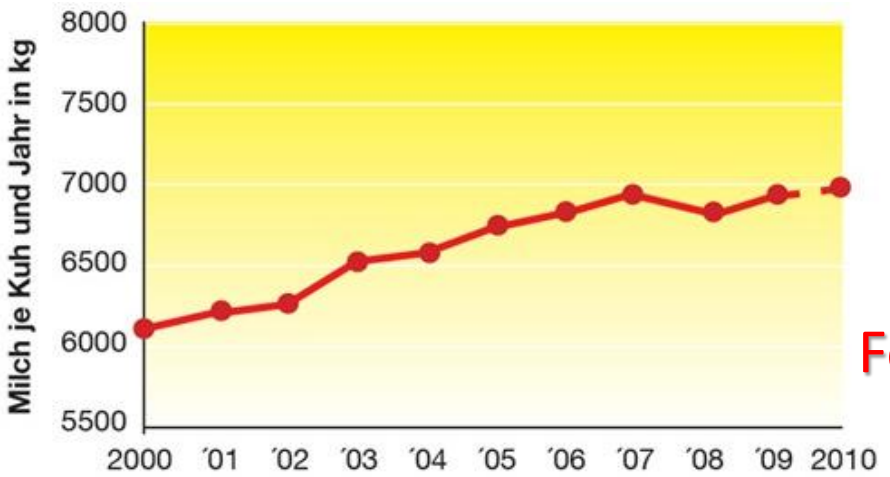
Early diagnosis of **Mastitis**

- importance of antioxidants?
- **Information from the udder lymph**?



Oxidative Stress

Milk yield of cows ↑ → metabolic activity of the udder ↑



Quelle: BMELV, Stat. Bundesmt, BLE

↓

Enhancement of oxygen turnover

↓

Formation of reactive oxygen species ↑

↓

Consumption and demand for antioxidants ↑

↓

- Forage quality and composition
- Supplementation on feed = poor
- Need recommendation???

Antioxidants

Trolox equivalent antioxidativ capacity (TEAC) (Miller et al. 1993)	**Antioxidant Capacity of Lipid-soluble Components (ACL) (Popov u. Lewin 1996)**	**Antioxidant Capacity of Water-soluble Components (ACW) (Popov u. Lewin 1994)**
Desferroxamin	Vitamin E (α-, β-, δ-Tocopherol, Tocotrienol)	Vitamin C
Bilirubin		Bilirubin
Harnsäure	Vitamin A und Provitamine (α-, β- , γ-, Carotine, Retionol, Retinsäure)	Liponsäure
Vitamin C		Melatonin
A-Tocopherol	Vitamin D	Albumin, Ceruloplasmin, Hemopexin, Haptoglobin, Glutathion, Aminosäuren
Glutathion, Albumin	Ubiquinol-10	
Mannitol, Glucose, Ethanol, Heparin, Harnstoff, Creatinin	Xanthine und Luteine	Glucose, Mannitol

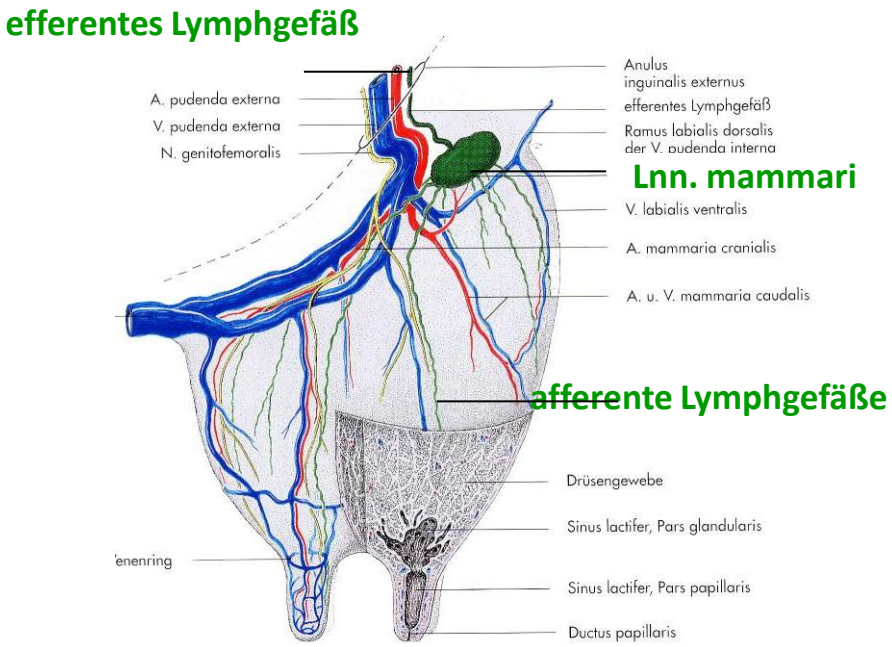
Lymphsystem der Milchdrüse

- Outline of the vessels in:

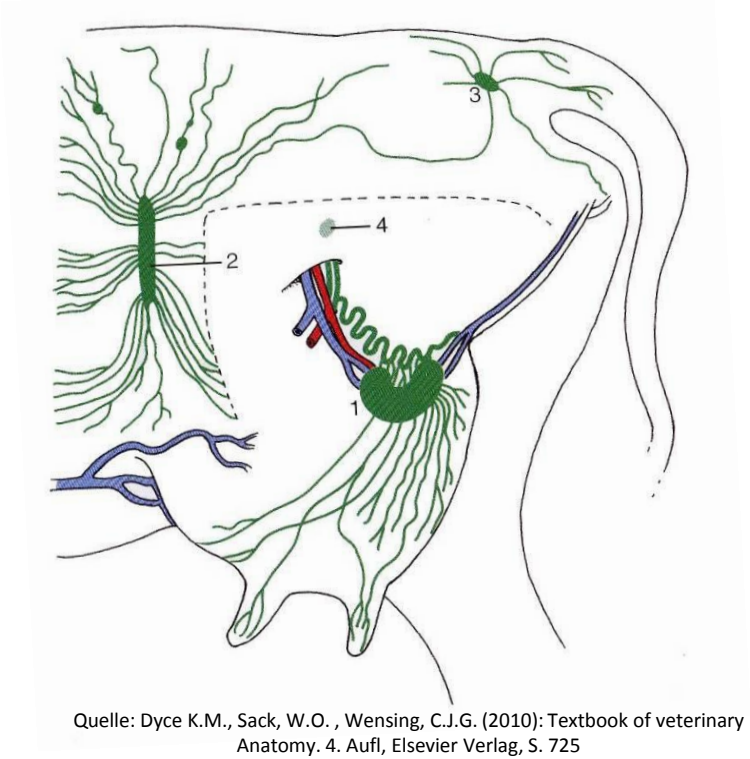
  parenchymatous, subcutaneous and

  Self-vessels of the teat

  (Ziegler u. Mosimann 1960)



Quelle: König, H.E., Liebig, H.G. (2008): Anatomie der Haussäugetiere. 4. Aufl., Schattauer, S.471



Quelle: Dyce K.M., Sack, W.O. , Wensing, C.J.G. (2010): Textbook of veterinary Anatomy. 4. Aufl, Elsevier Verlag, S. 725

- Transportation system for liquid and molecules from the interstitial space in the vascular system (Swartz 2001)

- Corresponds to composition interstitial fluid

Animals and methods

- Blood collection: vena caudalis median (tail vein)
- Lymph collection : puncture of peripheral (subcutaneous) afferent,

  lymphatic vessels at the surface of the caudo lateral udder

Animals and methods

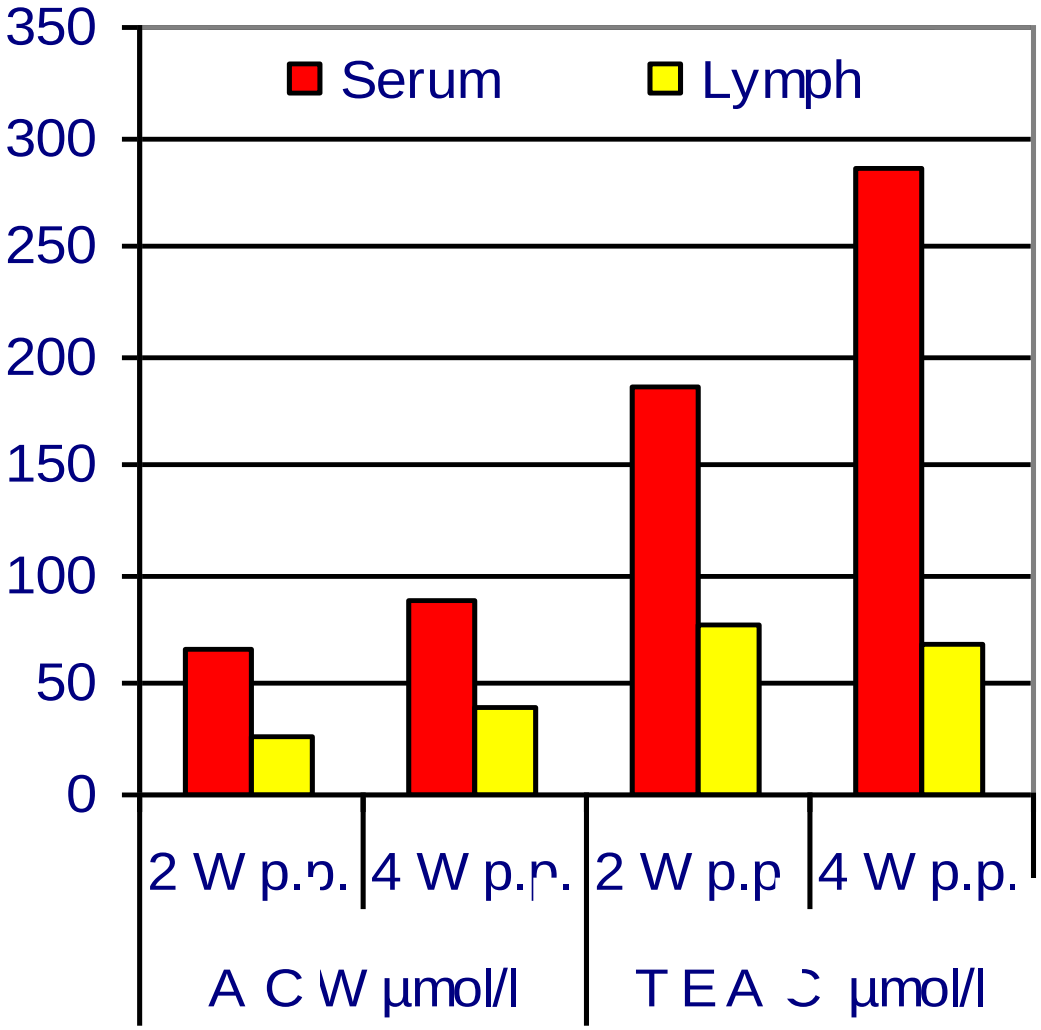
healty

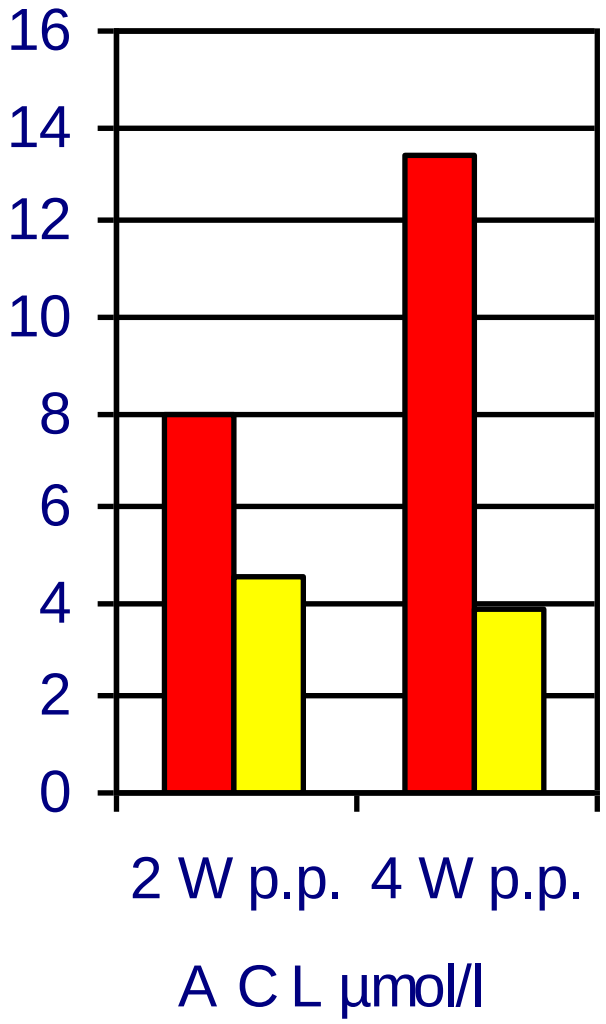
Lymph Blood Milch

acute, clinical Mastitis

Lymph Blood Milch

Antioxidants during lactation





AO - ascending in the blood, constant in the lymph

Mastitis and Se-lack!

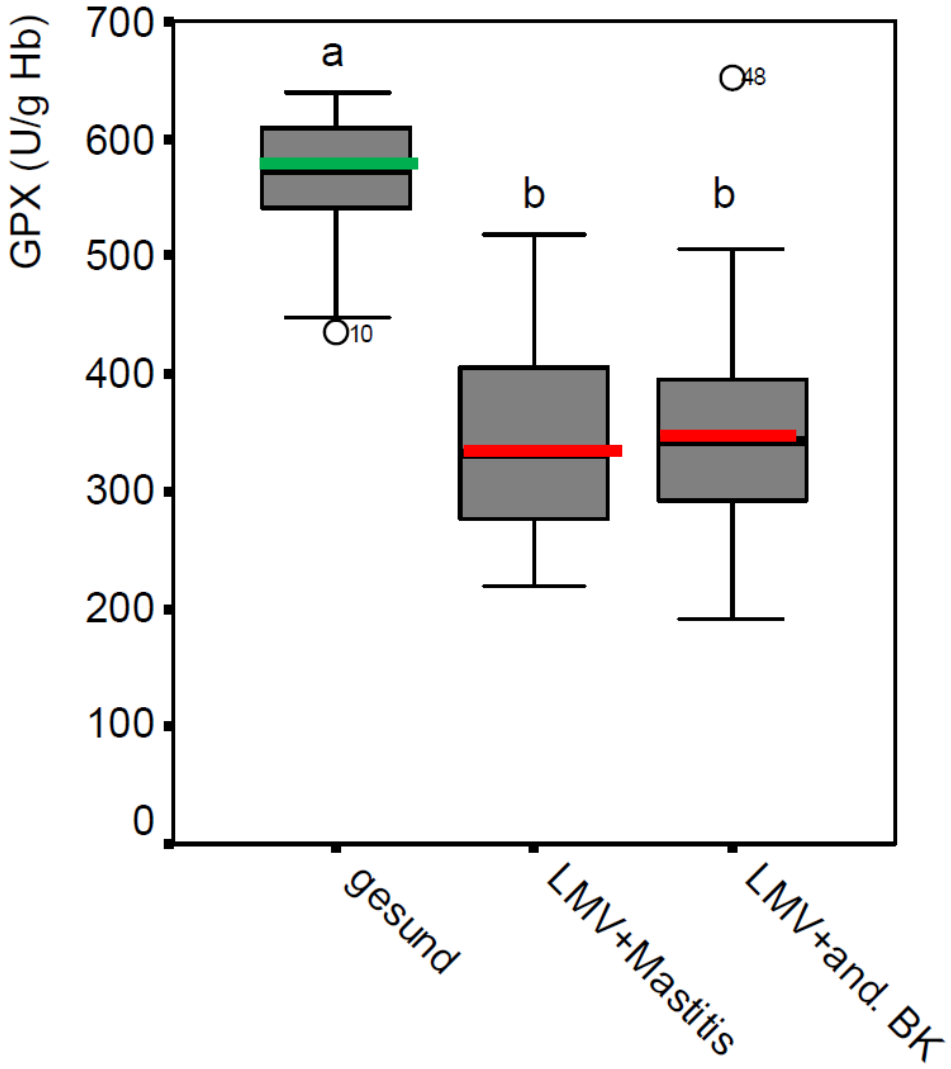
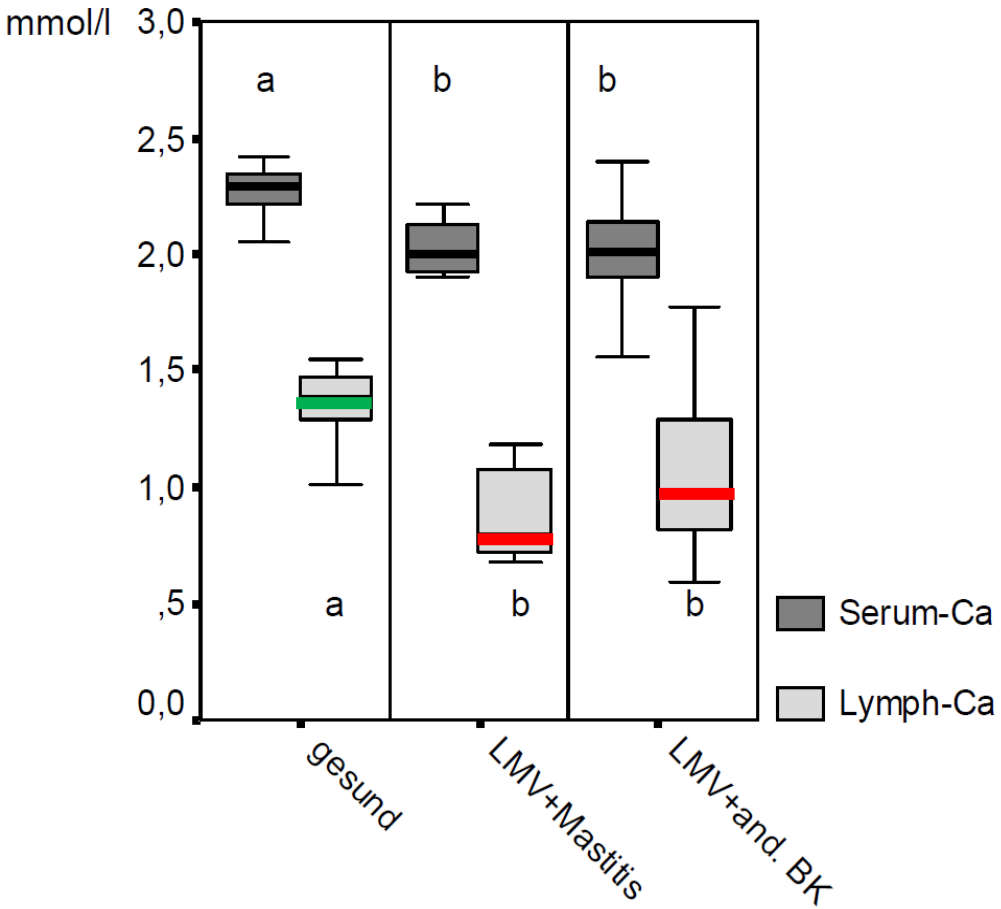


Abbildung 6: GPX-Aktivität (U/g Hb) im Vollblut bei gesunden und an LMV erkrankten DSB-Kühen mit und ohne Mastitis (unterschiedliche Buchstaben kennzeichnen signifikante Unterschiede zwischen den Gruppen)

Tabelle 25: ACL-Konzentrationen (µmol/l) im Blutserum und in der Euterlymphe bei gesunden und an LMV erkrankten DSB-Kühen mit und ohne Mastitis ($\tilde{x}$ (P_{25} - P_{75}), unterschiedliche Indices kennzeichnen signifikante Unterschiede innerhalb einer Zeile),

		gesund	**LMV+ Mastitis**	**LMV+ andere BK**
ACL µmol/l	Serum	8,47 (6,80 - 13,70)	8,57 (6,15 - 10,82)	7,61 (6,07 - 8,67)
	Lymphe	$4,52^{a}$ (3,65 - 6,22)	$2,58^{b}$ (2,01 - 4,06)	$2,22^{b}$ (1,64 - 3,74)
SP (Mann-Whitney-U-Test)		$p < 0,01$	$p < 0,01$	$p < 0,01$

Mastitis, ß-Carotin und Vitamin E !

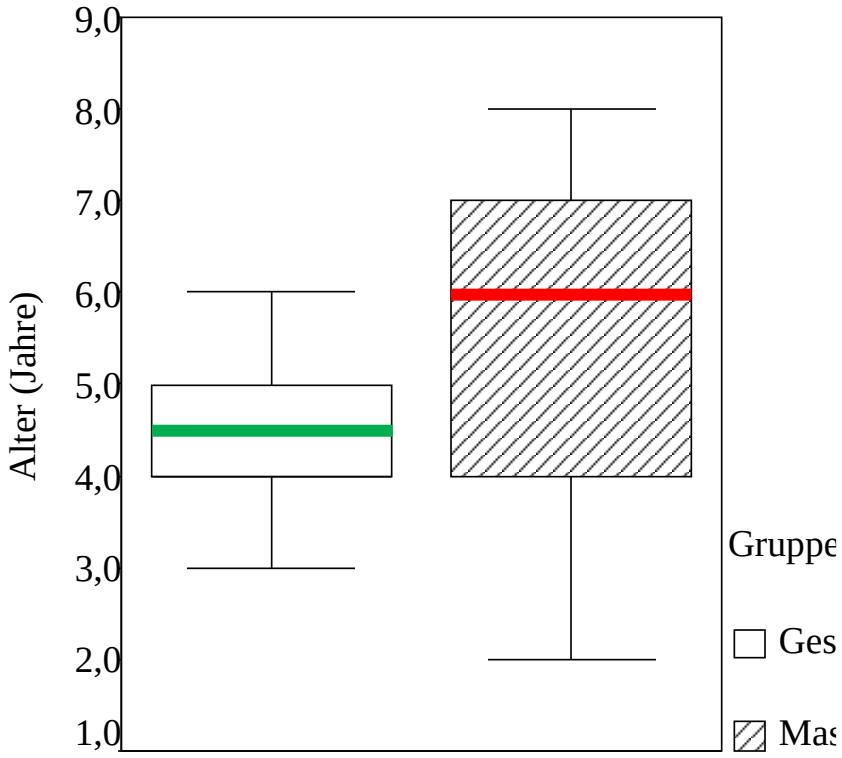


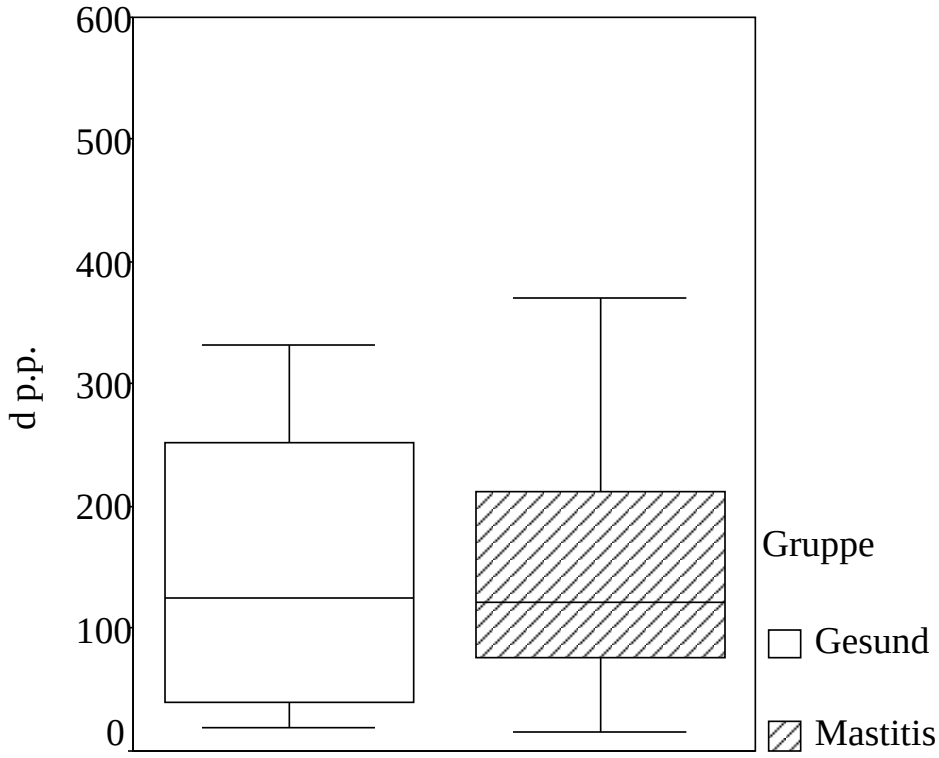
Mastitis and Ca !

Abbildung 9: Calciumkonzentrationen (mmol/l) im Blutserum und in der Euterlymphe bei gesunden und an LMV erkrankten DSB-Kühen mit und ohne Mastitis (unterschiedliche Buchstaben einer Zeile kennzeichnen signifikante Unterschiede innerhalb des Mediums)

Results

Age of cows and days p.p.

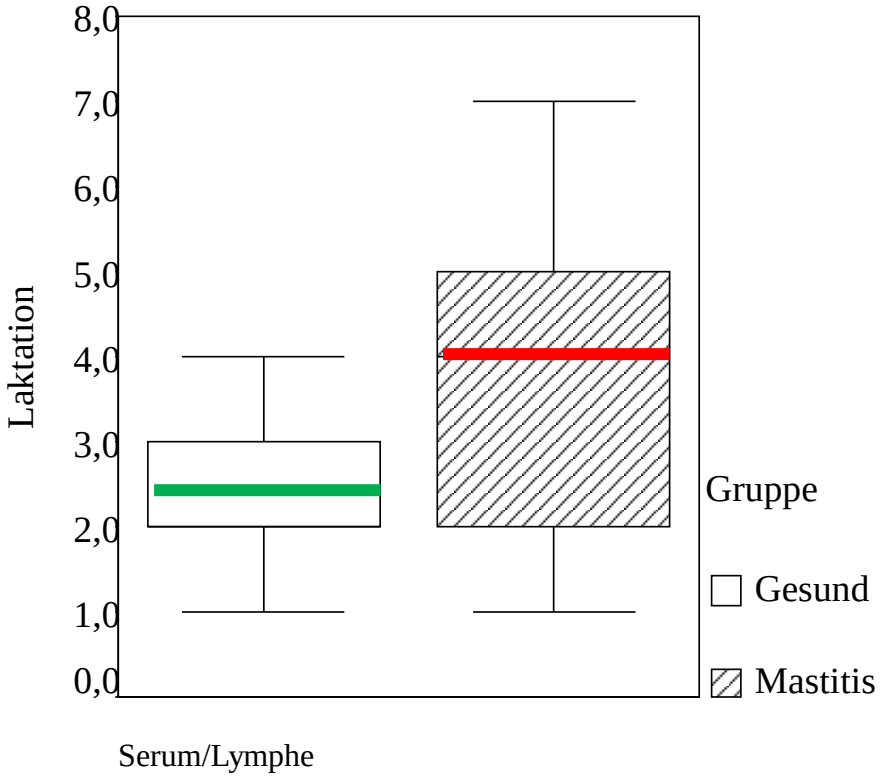


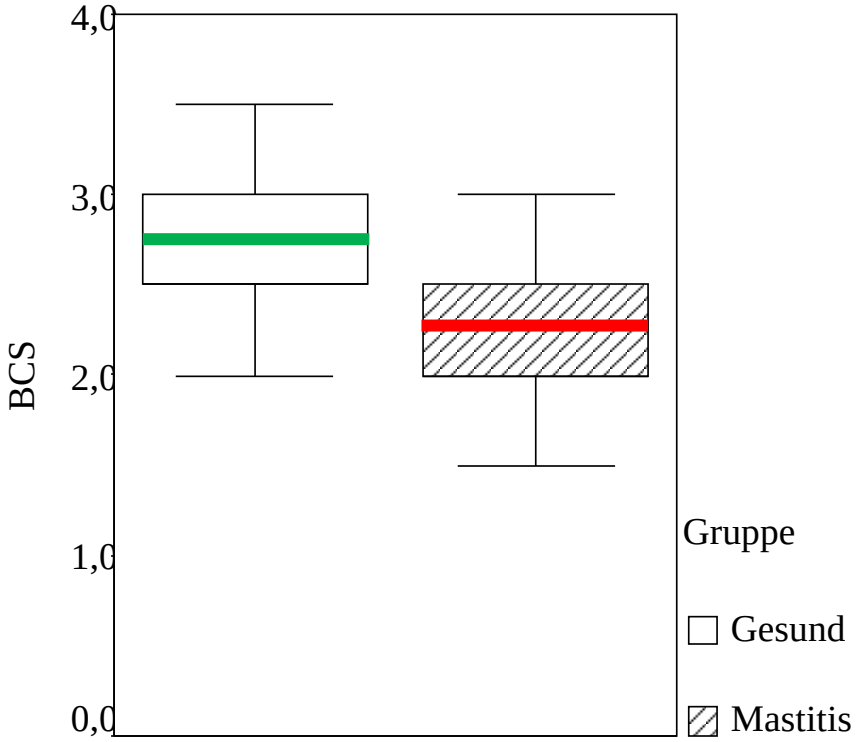


older cows

Hagen J, Sack U, Fürll M. Wien Tierärztl Mschr. 2011: 98; 25-32
Hagen J, Fürll M. Wien Tierärztl Monatsschr. 2010: 97,270-8

Results Lactation and BCS





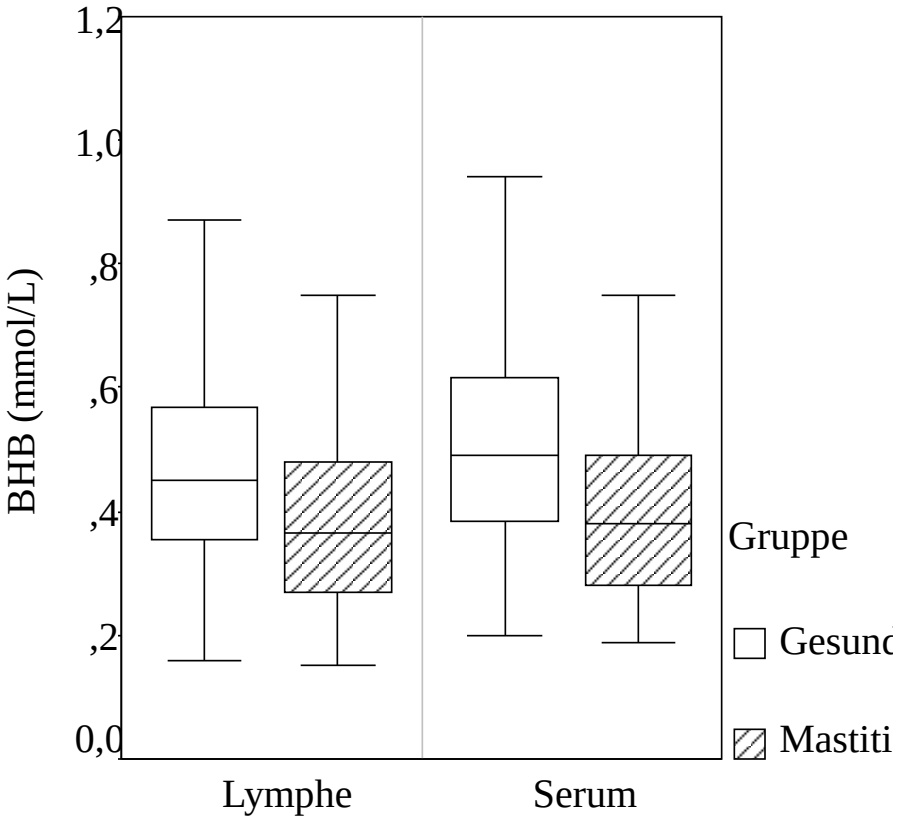
higher lactation
lower BCS

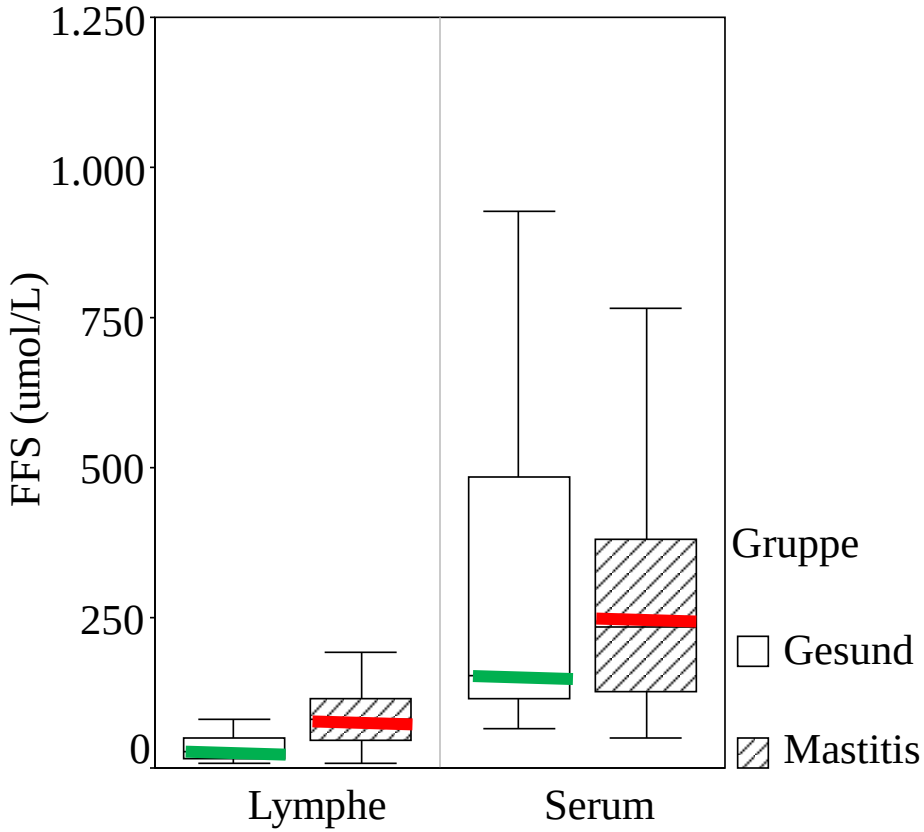
Hagen J, Sack U, Fürll M. Wien Tierärztl Mschr. 2011: 98; 25-32
Hagen J, Fürll M. Wien Tierärztl Monatsschr. 2010: 97,270-8

Results

BHB und FFS

Diss. Hagen 2011

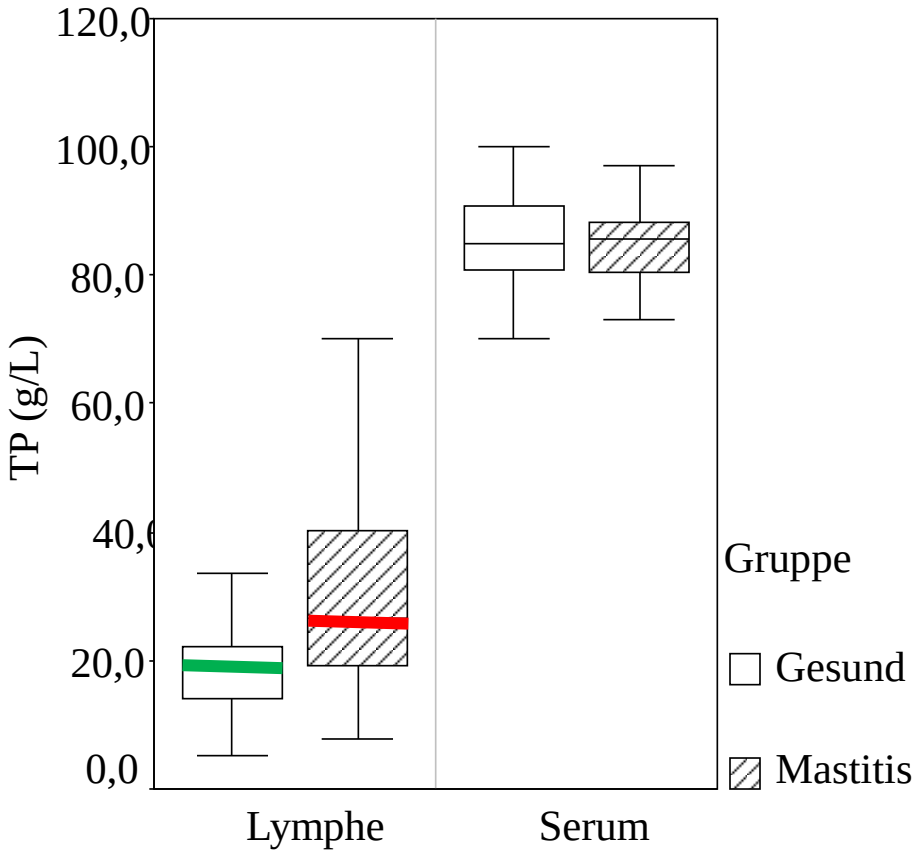


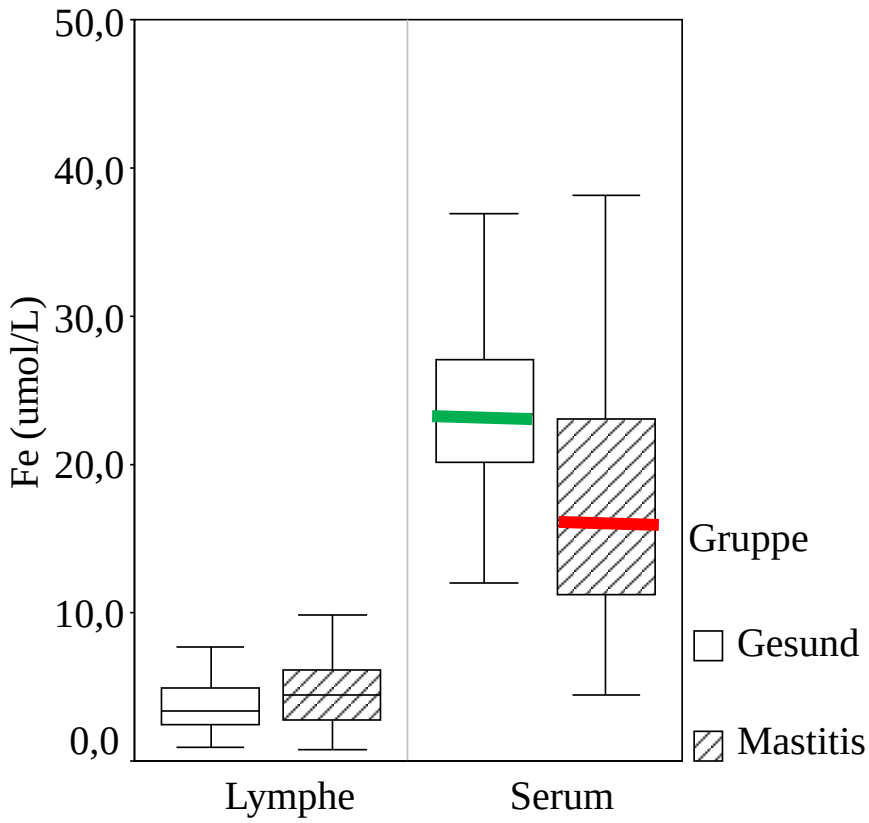


greater fat mobilization

Hagen J, Sack U, Fürll M. Wien Tierärztl Mschr. 2011: 98; 25-32
Hagen J, Fürll M. Wien Tierärztl Monatsschr. 2010: 97,270-8

Results Protein and Fe

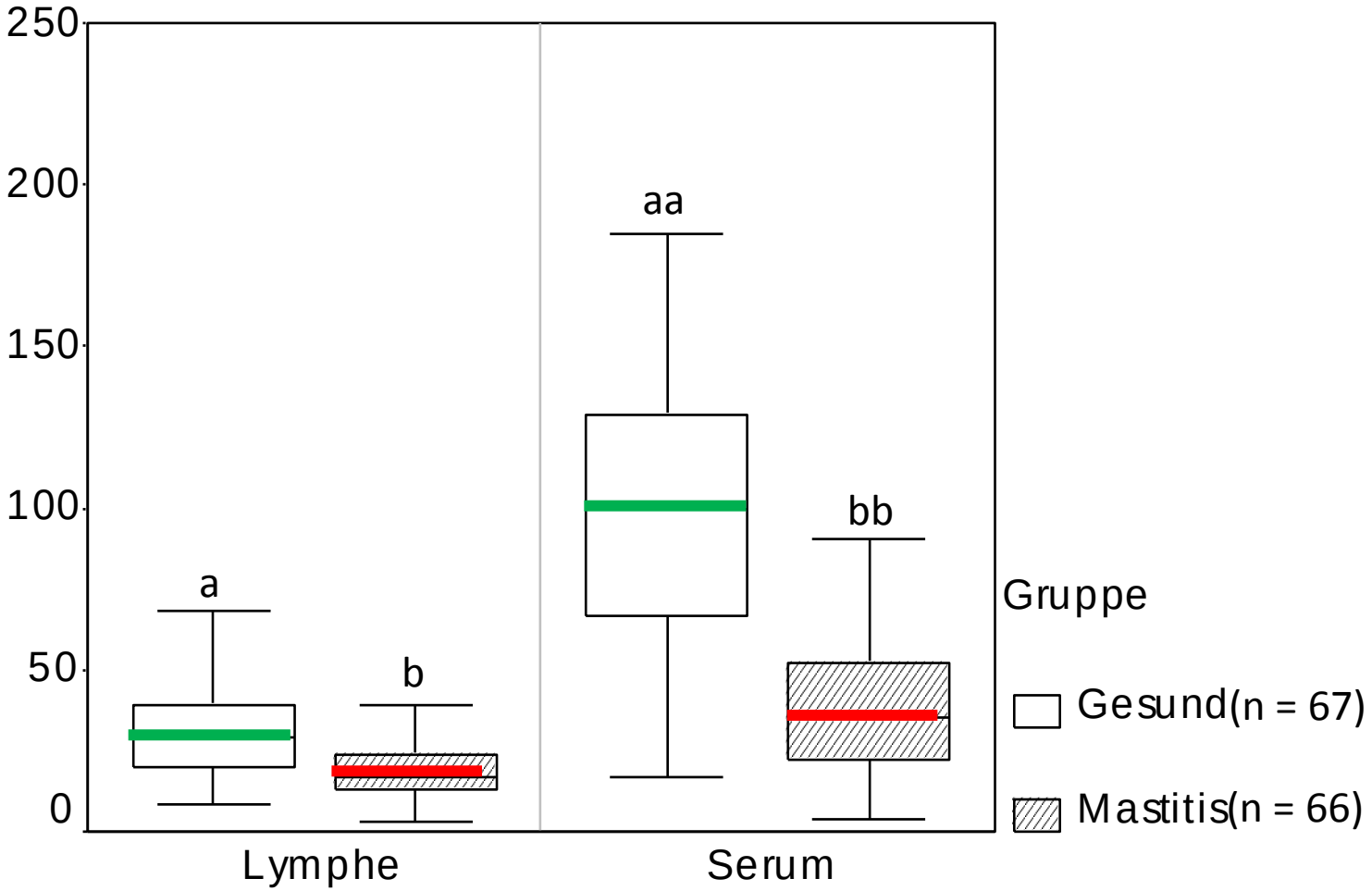




higher Protein
lower Fe

Hagen J, Sack U, Fürll M. Wien Tierärztl Mschr. 2011: 98; 25-32
Hagen J, Fürll M. Wien Tierärztl Monatsschr. 2010: 97,270-8

A C W (µmol/l)



a/b u. aa/bb → p < 0,0001; a/aa u. b/bb → p < 0,0001

fewer ACW

Hagen J, Sack U, Fürll M. Wien Tierärztl Mschr. 2011: 98; 25-32
Hagen J, Fürll M. Wien Tierärztl Monatsschr. 2010: 97,270-8

Vitamin E/ Selenium supplementation

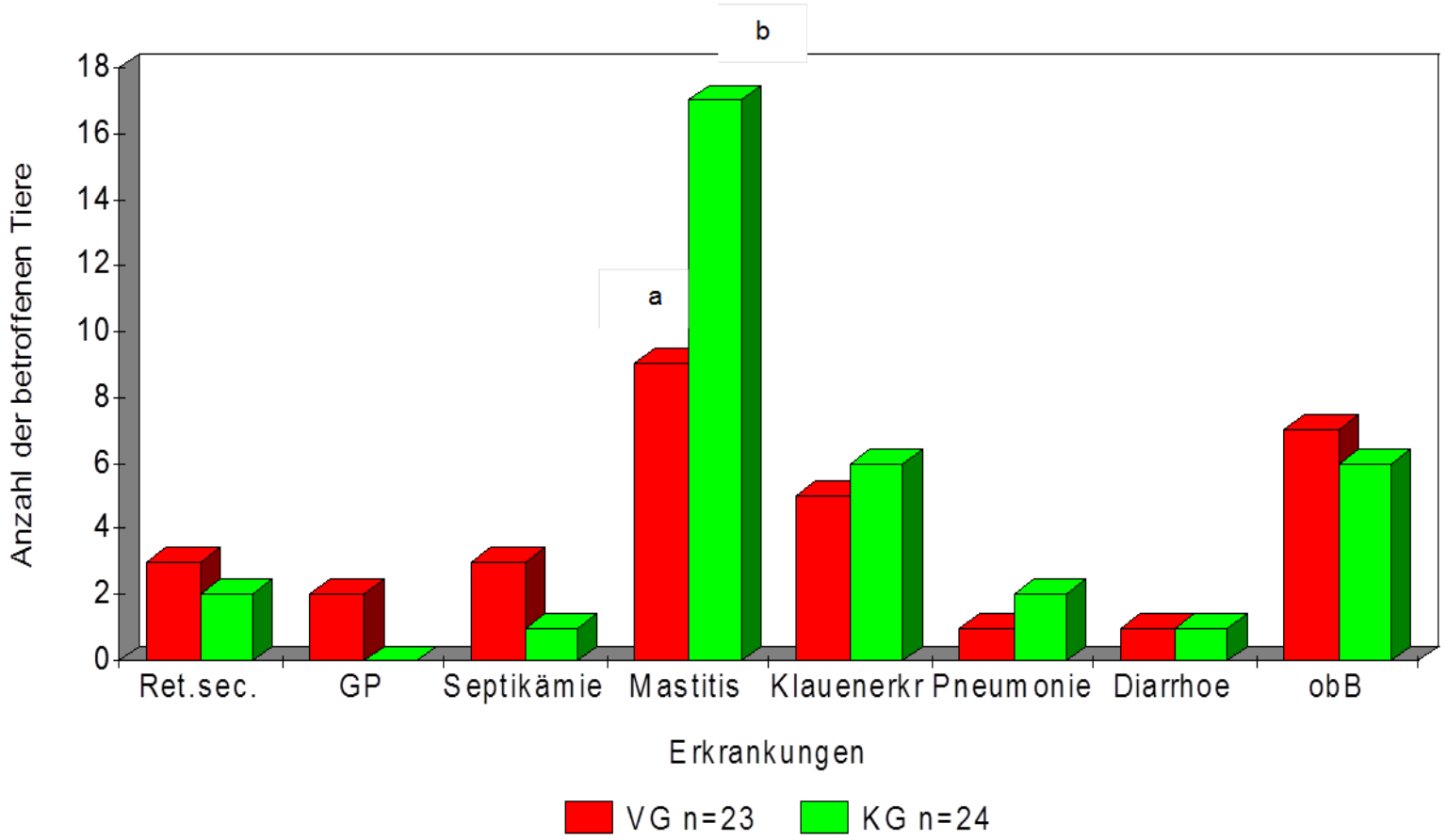
Experimental grupp VG

- Totale mixed ration
- Vitamin E und Selen enriched Minerals :
- **Selengehalt:0,5 mg/kg TS**
- **Vitamin E: 300 mg/kg TS = 447 IU/kg TM**

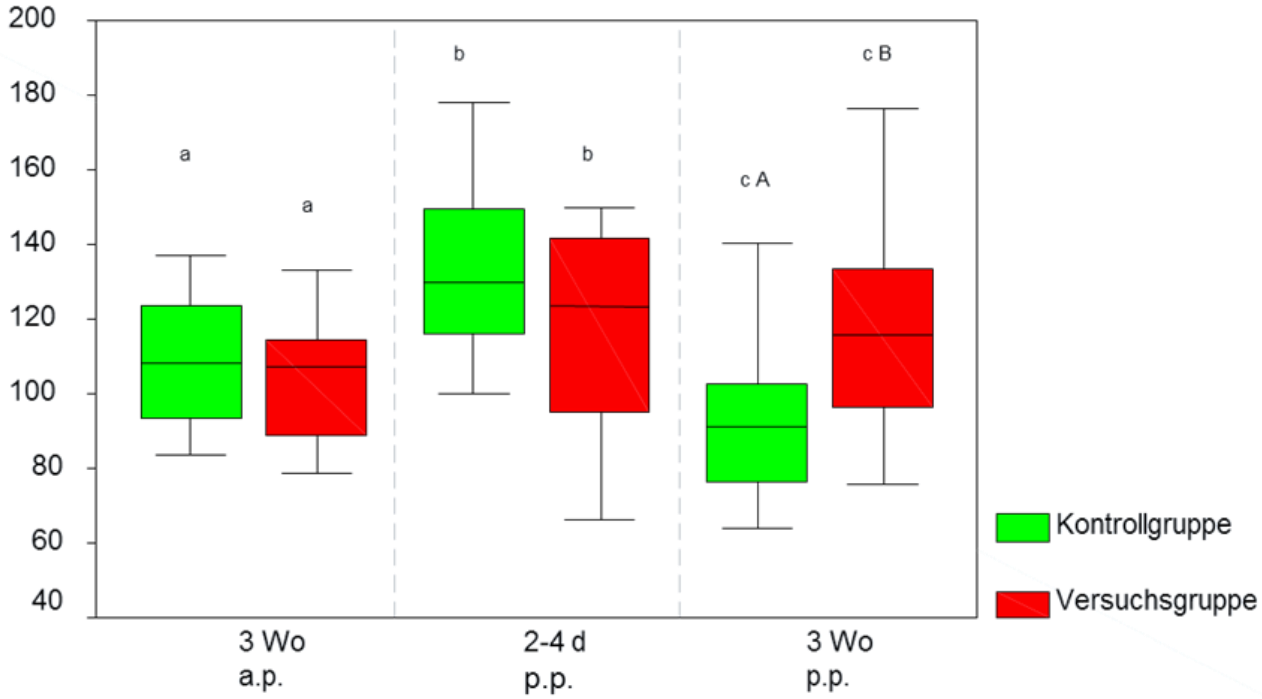
Control grupp KG

- Totale mixed ration
- **Selengehalt: 0,3 mg/kg TS**
- **Vitamin E: 75 mg/kg TS= 111,75 IU/kg TM**

Results- Morbidity (n)

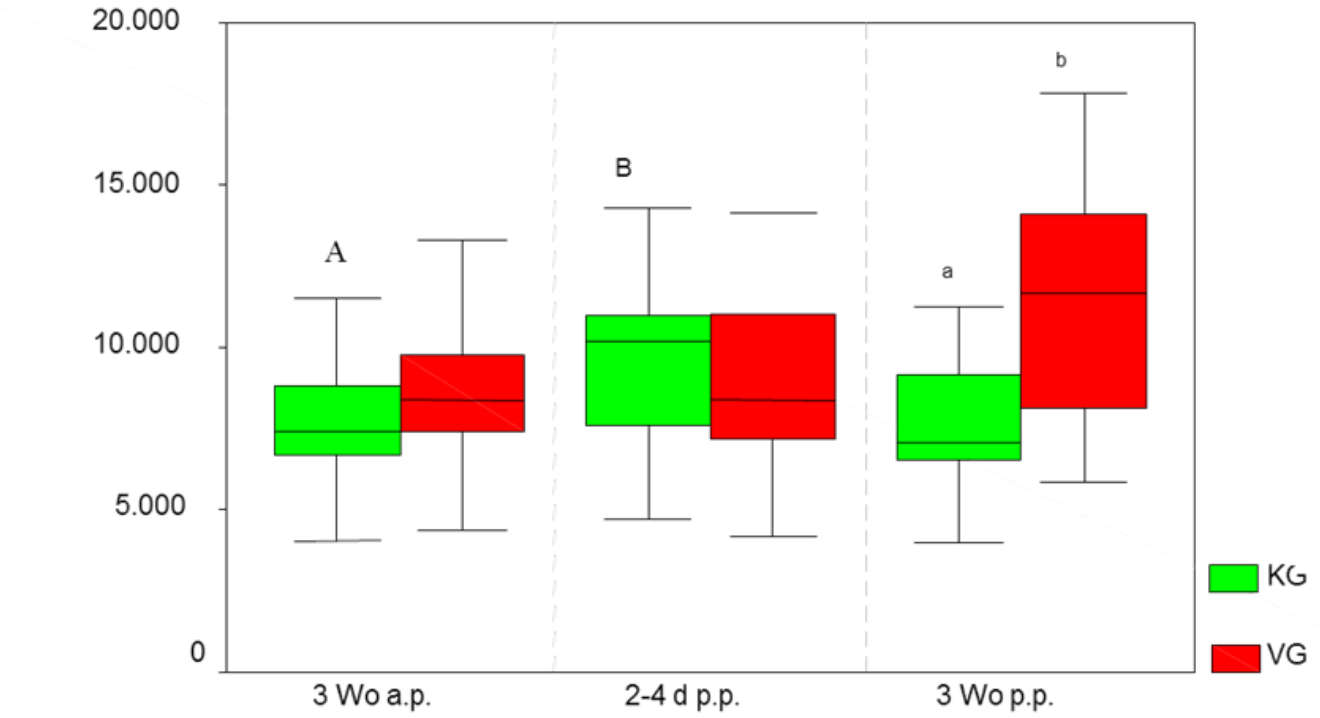


Results- GPX



GPX-Aktivitäten (U/gHk) in Versuchs- und Kontrollgruppe zur klinischen Wirksamkeitsprüfung einer mit Vitamin E und Selen angereicherten Mineralstoffmischung im peripartalen Zeitraum, Signifikanzen (p≤0,05) zwischen den Gruppen (A/B) und zwischen den Entnahmezeitpunkten (a/b/c)

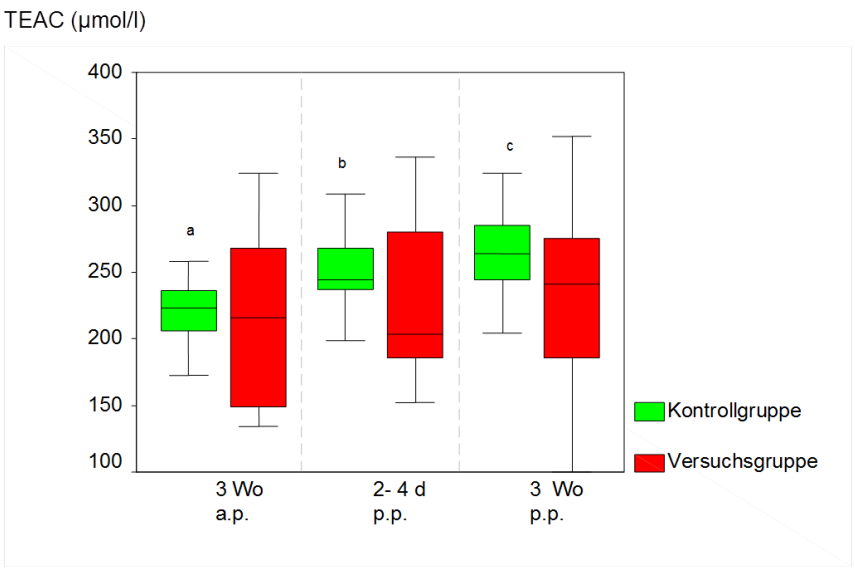
Results- SOD

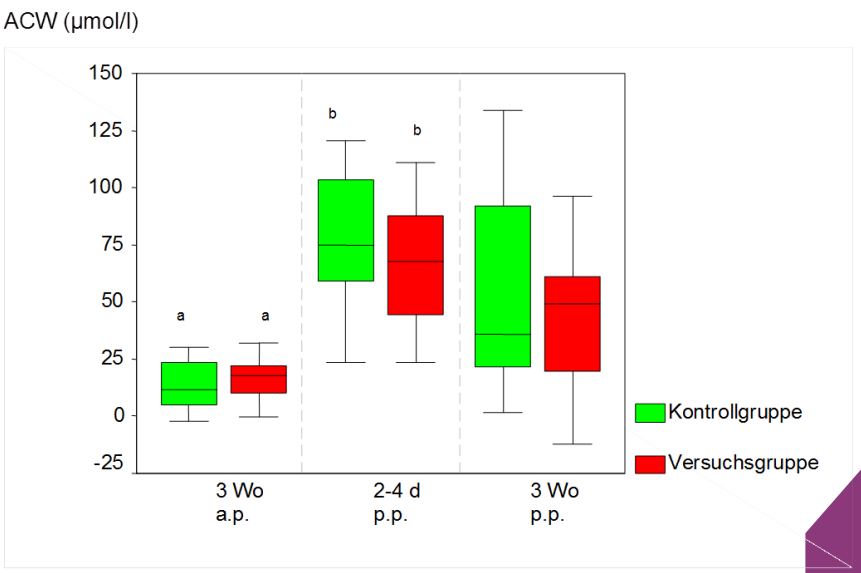


SOD-Aktivitäten (U/gHb) in Versuchs- und Kontrollgruppe zur klinischen Wirksamkeitsprüfung einer mit Vitamin E und Selen angereicherten Mineralstoffmischung im peripartalen Zeitraum, Signifikanzprüfungen (p≤0,05) zwischen den Gruppen (a/b)

Results - TEAC and ACW

TEAC





TEAC = Trolox equivalente of antioxidative capacity

ACW = water soluble antioxidative capacity

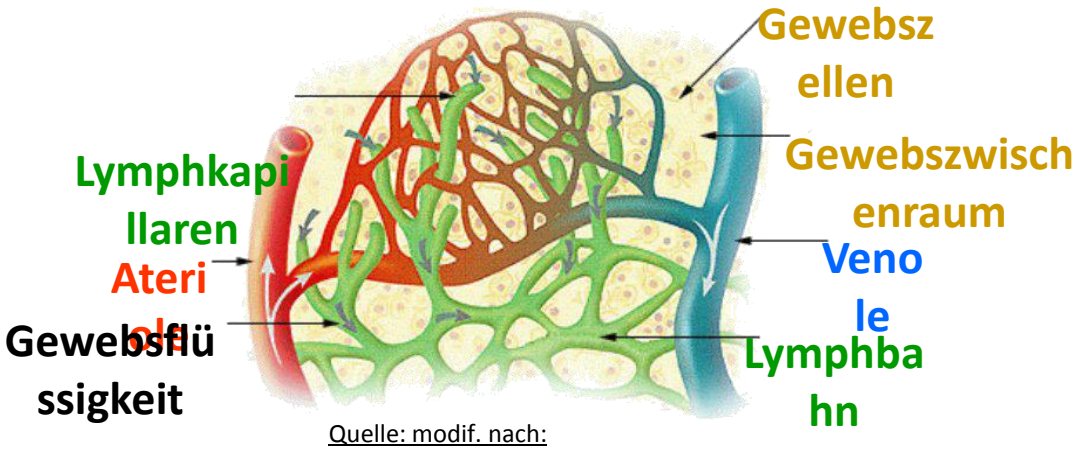
Summary

- Known mastitis risk factors: **acidosis, lipomobilisation, ketosis**, selenium / vitamin / antioxidant deficiency
- Immunologically are increased haptoglobin + TBFα
- AO p.p. rising in the blood, in lymph consistently
- by mastitis in lymph: **AO** (ACW, ACL, GPX) sign. ↓, like Fe, Mg, Ca -. **neutrophils, lymphocytes, monocytes** ↑↑
- no specific ↕ AO at different mastitis
- Vitamin E and Se supplementation reduce mastitis - ↑AO
- **Metabolic check in ↑ mastitis!**

Mastitis-Prophylaxis

. . . this includes :

- Vitamin E-, Se-, ß-carotin-substitution,
- stable energy metabolism
- stable Ca, Mg, Fe metabolism



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