Fertile 繁殖相关的

Literature review of the link between mastitis and fertility
奶牛乳房炎与繁殖的相关性信息汇总

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1. Proof of the link between mastitis and fertility

A series of epidemiological studies indicate that mastitis has a negative effect on fertility

- Cows with mastitis showed 乳房炎奶牛表现出：
  - More days not pregnant on farm (140 vs. 88; p<0,05) (Ahmadzadeh et al., 2009.) 空怀天数增加（140 vs 88, p<0.05）
  - Lower conception rate 受胎率降低  (Santos et al., 2004.; Hertl et al. 2010. Lavon et al; 2011; Fuenzalida et al., 2015)
  - Increased day to first service 首次配种天数增加 (Barker et al. 1998)
  - Less estrus expression 发情表现减弱  (Hockett et al. 2005.)
  - Increased early abortion rate 胚胎早期死亡增加 (Moore et al., 2005)
  - Irregular interrestrus interval 发情周期不规律 (Moore et al., 1991)
1. Proof of the link between mastitis and fertility

Lavon et al. 2011

- Records from 287,192 AI of 151,481 cows from 222 farms throughout Israel
- Infection and cure based on cell count records
- Elevation in SCC decreased the probability of conception relative to that of uninfected cows.

Elevation in SCC decreased the probability of conception relative to that of uninfected cows.
1. Proof of the link between mastitis and fertility

乳房炎和繁育

The link between mastitis and fertility is proven,
目前已经证实以下方面

For

- **a** • All major pathogens 所有病原菌
- **b** • All severities of mastitis 任何严重程度
- **c** • Before and after insemination 输精前、后
Barker et al., 1998

- Days to first Al increased (93.6d vs 71d; p<0.01)
- 首配天数增加(93.6d vs 71d; p<0.01)
- Higher number of Al per conception (2.9 vs 1.6; p<0.01)
- 更多的输精次数(2.9 vs 1.6; p<0.01)

No difference in effect on fertility when mastitis was caused by gram neg or gram pos

无论革兰氏阳性球菌还是阴性杆菌，对繁殖的负面影响上面没有差异

The link between mastitis and fertility is proven, independent of severity of the mastitis. For:

- **a**: Intramammary pathogen
  - 乳房内病原菌
- **b**: Severity of the mastitis
  - 严重程度
- **c**: The timing relative to insemination
  - 输精相关时间
1b. Severity of the mastitis 乳房炎严重程度

**Influence of severity 严重影响程度**
- 3277 first AI’s of cows on 4 farms in Wisconsin, US
- 威斯康星4个牧场的3277个首配数据
- Odds of pregnancy was reduced by about 30 and 50% for cows with mild and moderate-severe cases of clinical mastitis
- 患有轻度和中度临床乳房炎可使怀孕比率下降30%和50%。

Fertility also affected in cases of mild mastitis!
轻度临床乳房炎也会影响繁育性能

Fuenzalida et al., 2015. The association between occurrence and severity of subclinical and clinical mastitis on pregnancies per artificial insemination at first service of Holstein cows. J Dairy Sci. 98:1-15
Even subclinical mastitis has an effect

- Schrick et al. 2001
- Data from 1986 to 1997, 752 cows
- 数据来源于1986-1997年的752头牛

1c. The timing relative to insemination

<table>
<thead>
<tr>
<th>CM BEFORE first AI 輸精前</th>
<th>CM AFTER first AI 輸精后</th>
</tr>
</thead>
</table>
| **Longer calving to first AI interval (95,2** vs 75,9*) 首配天数延长** | **Longer calving to conception (119,1** vs 94,1*)**
| **Longer calving to conception (141,7 ***vs 94,1*): larger effect** | **Longer calving to conception (119,1** vs 94,1*)**
| **More services to conception (2,1 vs 1,8 ; not significant)** 輸精次数增多 | **More services to conception (3,4** vs 1,8*): larger effect 輸精次数更多，影响更明显** |

Also when the mastitis occurred after confirmed pregnancy, it may have an effect on the survival of the embryo/fetus

- 2087 cows
- 60 clinical cases of mastitis
- 127 cases of abortion
- No bacterial cultures

Outcomes

- Cows with clinical mastitis in the first 45 days of gestation were almost 3 times more likely to abort within next 90 days
- In pregnancy, cows with clinical mastitis in the first 45 days of gestation were almost 3 times more likely to abort within next 90 days

2. The mechanisms behind 背后的机制

- **a**  The PGF2α- story 前列腺素的故事
- **b**  Hypothalamus- pituitary axis 下丘脑-垂体轴
- **c**  Direct effect on the follicle 对卵泡的直接影响
- **d**  Sickness 疾病
2a. The PGF2α- story 前列腺素故事

1. Endotoxines induce inflammation 内毒素产生炎症反应

2. Higher plasma levels of prostaglandines and other pro-inflammatory cytokines
   - Also PGF2α increased
   - 血浆中前列腺素和其他炎症介质含量增多，PGF2α也增多

3. Stimulant effect of PGF2α on uterine smooth muscles contractions
   - Early luteolysis
   - PGF2α能够收缩子宫平滑肌；早期的黄体溶解

4. Gradual decline in progesterone levels 孕酮水平逐渐降低
   - Abortion or embryo- resorption in early lactation 早期的流产或胚胎吸收
   - Shortened estrus intervals 发情间隔缩短

2b. Hypothalamus- pituitary axis 下丘脑-垂体轴

- **Mastitis (due to bacterial material, cytokines or pain)** induces CRH → ACTH → cortisol 乳房炎（细菌、细胞因子或疼痛）诱导CRH → ACTH → 皮质醇

- **It has been proven that ACTH reduces the basal LH pulses → slower follicular growth**已经证实促肾上腺皮质激素降低促黄体生成素的释放，延缓卵泡发育


2c. Direct effect on the follicle 对卵泡的直接作用

- Inflammation reduces the ability of the follicle to produce estradiol → does not trigger an appropriate LH surge → no or delayed ovulation

- 炎症降低卵泡生成雌二醇的能力→不会引起合适的LH释放→延迟排卵或不排卵

Lavon et al. 2010. Naturally occurring mastitis effects on timing of ovulation, steroid and gonadotrophic hormone concentrations and follicular and luteal growth in cows. J. Dairy Sci. 93:911-921
In addition, the follicle enclosed oocyte is highly sensitive to inflammation

- Sensitive to hormonal dysbalances
- Oocyte is also highly sensitive to cytokines or toxines
  - disruption of oocyte maturation
  - Disruption of embryonic development. (Soto et al. 2003)
  - 胚胎发育受到干扰

Oocytes from cows with high cell count had a 4 times lower chance to develop into a day 7 blastocyst (p<0,05)

2d. Sickness 疾病

- Early lactation is the period with the highest incidence of mastitis 泌乳早期乳房炎高发
- Also the most challenging period for the metabolism of the cow. 代谢病也是大问题
- All high producing cows experience negative energy balance (NEB) during early lactation 高产奶牛经历能量负平衡
- Appetite and feed intake reduce due to pain, also in mild mastitis (Sepulveda-Varas et al., 2014) 乳房炎会疼痛，食欲和采食量会降低
- It is generally accepted that NEB and concurrent weight loss is disastrous for fertility 能量负平衡和体重丢失对繁殖影响很大

→ Any event that will increase the NEB may have an extra detrimental effect on the
4. The effect of NSAIDs
非甾体抗炎药的作用

Mastitis affects fertility 乳房炎影响繁殖

- Reduce mastitis incidence 降低乳房炎发病率
- Reduce the effect mastitis has on reproduction 降低乳房炎对繁殖的影响

NSAIDs 非甾体抗炎药

- Reduction inflammation 降低炎症
- Reduction pain 降低疼痛
Cows with mastitis were 42% less likely to be culled when Metacam® was added to standard antibiotic therapy (p<0.001).

**THE MAMMARY STUDY**

**727 cows across New Zealand**
with mild and moderate cases of clinical mastitis

**Meloxicam vs placebo**
in combination with standard antibiotic therapy

**28.2%**

**16.4%**

Cows with mastitis were 42% less likely to be culled when Metacam® was added to standard antibiotic therapy (p<0.001).
The reasons for culling suggested a fertility link. Cows treated with Metacam® were less likely to be culled for not being pregnant (p=0.02).

<table>
<thead>
<tr>
<th>Reasons for culling</th>
<th>Metacam®</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown 未知</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Low production 低产</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mastitis 乳房炎</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Three titer 瞎乳区</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surplus to requirements 主动淘汰</td>
<td>18</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>Not pregnant 未孕</td>
<td>8</td>
<td>20</td>
<td>28</td>
</tr>
<tr>
<td>Udder breakdown 乳房结构差</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Old age 老龄</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other causes 其他</td>
<td>8</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>39</strong></td>
<td><strong>67</strong></td>
<td><strong>108</strong></td>
</tr>
</tbody>
</table>
Hypothesis 猜想

- Inflammation such as mastitis inhibits fertility 乳房炎会抑制繁殖
- Not pregnant → more likely to be culled 未孕→ 很可能被淘汰
- By reducing inflammation, cows were more likely to have a

Note: New Zealand is a highly seasonal system: cows not on

失败受孕是全球淘汰奶牛的最重要的单一性因素

Failure to conceive is globally the single most important
reason to cull a dairy cow

受孕失败是淘汰奶牛的最主要的单一性因素
THE FERTILE STUDY WAS DESIGNED TO INVESTIGATE this question

随后进行的繁殖研究将会澄清这个疑问

THE FERTILE STUDY 繁殖研究

Over 500 cows across 6 European countries with mild and moderate cases of clinical mastitis

Meloxicam vs placebo in combination with standard antibiotic therapy

欧洲6个国家的500余头患轻中度临床乳房炎奶牛

美达佳配合抗生素进行治疗
Fertile study 繁殖研究

使用2-4支优孢新治疗轻、中度临床乳房炎
配合使用美达佳或空白对照

首次治疗前细菌培养

首次治疗细菌培养

在此阶段统计细菌学治愈率

Breeding information
- Service dates and numbers
- Pregnancy checks and outcomes

Service
1 2 3
Pregnancy check

Fate of the animals

Culling?

Days after diagnosis
确诊后天数
FERTILE results revealed: 繁殖研究结果显示:
Metacam® improves fertility in dairy cows with mastitis
美达佳能够改善因乳房炎导致的繁殖障碍

The addition of Metacam® to standard antibiotic therapy: 美达佳配合抗生素治疗能够:

- increased first-service conception rate
  提升首次配种率

- decreased the number of inseminations required to conceive
  减少配种次数

- increased probability of pregnancy at 120 days after calving
  增加120天后怀孕率

Adding Metacam® also: 使用美达佳也可以:

- led to a higher bacteriological cure rate
  提升细菌学治愈率
Meloxicam therapy resulted in a higher proportion of cows conceiving from their first insemination. (*)p<0.01
The number of inseminations required to achieve pregnancy was significantly lower in the Meloxicam® group (*p<0.01).
Fertile study: greater probability of pregnancy
繁殖研究：怀孕率更高

At 120 days after calving, more cows were pregnant in the Meloxicam group
美达佳组牛仔产犊后120天的怀孕率更高

(*p<0.01)
Fertile study: Higher bacteriological cure rate
繁殖研究：更高的细菌学治愈率

First Service conception rates?

Metacam® cows have a higher bacteriological cure rate than control cows
美达佳治疗组的细菌学治愈率更高

(*p<0.05)
Conclusion 结论

Mastitis reduces fertility significantly 乳房炎会明显降低繁殖性能
  • In gram positive and negative mastitis 无论哪种类型的细菌
  • In both mild and severe mastitis 无论轻度还是重度
  • Before and after insemination 无论输精前还是输精后

There are several mechanisms by which this can be explained 有几种机制
  • All inflammation related 全部是炎症相关

Treating mastitis with meloxicam 使用美洛昔康治疗乳房炎
  – Can mitigate the negative effect of the mastitis 能够缓和乳房炎的负面效应
  – Offering some long-term benefits 带来长期的效益