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Kick-starting ovarian cyclicity by using dietary glucogenic precursors in post-partum dairy cows: a review

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ABSTRACT
The objective of this review is to describe how dietary glucogenic precursors could stimulate ovarian activity in post-partum dairy cows and improve reproductive success. Although the nutrient requirements for the early resumption of ovarian cycles, and for follicle and embryo development are quantitatively small, reproductive success is deteriorated by post-partum negative energy balance. Since very little glucose is absorbed directly from the digestive tract of ruminants one of the targets for nutritional manipulation could be the glucogenic potential of the diet. This could be achieved by giving rumen-resistant starch or mono-propylene glycol. Both these adaptations increase glucose, insulin and insulin-like growth factor-1 plasma concentrations and stimulate ovarian follicle growth.

1. Introduction
The objective of this review was to describe how dietary glucogenic precursors could stimulate ovarian activity in the post-partum (PP) dairy cow and improve reproductive success. As a result of increases in milk production obtained through advances in genetic selection and improved husbandry, reproductive efficiency in dairy cows has declined between 1975–1982 and 1995–1998 from 55.6% to 39.7% [1]. Although this negative trend has recently bottomed out and reproduction has begun to improve due to the inclusion of fertility traits in selection programmes [2], modern dairy cows still require an additional 30d to conceive when comparing results between 1999 and 2010 [3].

Feeding dairy cattle should always be optimized to cover requirements for milk production and maintain good health but it also may be possible through the choice of certain feedstuffs to target a particular physiological function, such as reproduction. The idea of targeting certain aspects of metabolism to stimulate reproduction in dairy cows was first proposed nearly twenty years ago with the use of glucogenic vs. lipogenic diets [4]. Further research has since been conducted.

The first section of this paper will outline the general metabolic context of the dairy cow PP. The second part will describe the rationale behind modifying the diet PP. The final section will describe how glucogenic supply can be increased to improve reproductive success.

2. Metabolism in the post-partum dairy cow
In the dairy cow, the negative energy balance (NEB) occurs PP [5] because the increase in feed intake after parturition, is not able to keep up with the rapid rise in energy requirements for milk production [6] even though the cows are fed ad libitum. The requirements for energy and protein of an average European dairy cow at peak milk production are multiplied by 3 to 5 compared to late gestation [7] and the peak in nutrient requirements occurs earlier (at 1 to 2 months PP) compared to the peak in feed intake (at 3 to 4 months PP) therefore inducing NEB [7]. The problem is physiological in relation to a lag in feed intake compared to nutrient requirements.

NEB can also exist in beef cattle PP but the situation is different compared to dairy cows because beef cows are often managed in low input systems. Nutrient requirements are not as high PP but farmers often use low quality forages or limit cow access to good quality forages therefore inducing NEB [7]. The problem is due to the farmer trying to reduce production costs by limiting nutrient intake compared to nutrient requirements.

As a result of NEB, insulin decreases and growth hormone (GH) increases during this period to promote lipolysis [8]. Despite high circulating GH, there is a decrease in insulin-like growth factor-1 (IGF1) because insulin is low and is no longer able to stimulate the expression of the GH receptor 1A. Without this receptor GH cannot stimulate IGF1 production. The somatotropic axis is said to become “uncoupled”
3. Glucose precursors to improve reproductive efficiency

Changing the composition of the diet or adding mono-propylene glycol (MPG) can increase glucose precursors. The papers published on the effect of a glucogenic supplement (starch or MPG) on reproductive function are summarized in Tables 1–3.

### 3.1. Peri-partum period (ketosis and immunity)

A recent meta-analysis showed that the interval between calving-to-first-service was 8 d longer and calving-to-conception was 16 to 22 d longer in cows with subclinical ketosis [24]. In periparturient dairy cows, MPG increased insulin and glucose while decreasing NEFA and BHB [25] and reduced the triacylglycerol content of the liver [26]. Therefore, MPG...
Table 2. Summary results of the effect of a dietary glucogenic supplement in the form of mono-propylene glycol (MPG) on reproductive function in non-grazing post-partum dairy cows.

<table>
<thead>
<tr>
<th>Basal diet</th>
<th>Basal diet starch and source</th>
<th>Amount of glucogenic supplement (g or ml/cow/d)</th>
<th>Duration of suppl. (days)</th>
<th>No. Cows/treatment</th>
<th>Metabolic effects</th>
<th>Energy balance</th>
<th>Effect of suppl. on reproductive parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMR maize silage</td>
<td>TMR maize silage</td>
<td>Basal diet maize starch 21% 0 ml 250 ml 0 g 225g MPG + 225 g Ca propionate</td>
<td>Between 3–15d PP During 6 wk PP</td>
<td>9</td>
<td>- - - -</td>
<td>1</td>
<td>ICO → ICAI ↓ CR at 1st AI →</td>
<td>(82)</td>
</tr>
<tr>
<td>TMR maize silage</td>
<td>TMR maize silage</td>
<td>Basal diet maize starch 20% 0 ml 300 ml</td>
<td>3 to 8d of induced oestrus at 60 DIM</td>
<td>13</td>
<td>- - - -</td>
<td>-</td>
<td>At 90d PP number of acyclic cows ↓</td>
<td>(84)</td>
</tr>
<tr>
<td>TMR</td>
<td>Basal diet maize starch 15% 0 ml 500 mL</td>
<td>Between 7 and 42d PP</td>
<td>16–17</td>
<td>1 ↑ 1 ↓ 1 ↓</td>
<td>No difference between groups</td>
<td>ICO ↓ length of 1st luteal phase 1 (13.1 vs. 7.3d)</td>
<td>(25)</td>
<td></td>
</tr>
<tr>
<td>TMR prepartum 66%/33% grass silage or hay/maize silage PP 33%/66% grass silage or lucerne hay/maize silage</td>
<td>Basal diet maize stalk 15% 0 ml 500 ml</td>
<td>Between 7 and 40d PP</td>
<td>17–18</td>
<td>1 ↑ 1 ↓ 1 ↓</td>
<td>No difference between groups</td>
<td>P4 recovery → CR 1st AI → CR at 15d PP → Number of AI/conception →</td>
<td>(85)</td>
<td></td>
</tr>
<tr>
<td>50%/50% maize silage/alucone hay + concentrates for milk production</td>
<td>Basal diet maize stalk 15% 0 ml 300 mL</td>
<td>Holstein cows at maintenance</td>
<td>17 from start of synchronization and superovulation until after 2nd AI (embryos collection 6d after 2nd AI)</td>
<td>28</td>
<td>1 ↑ 1 ↓ 1 ↓</td>
<td>Improved</td>
<td>No effect on follicle dynamics no effect on LH secretion characteristics no effect on oocytes collected and their quality</td>
<td>(86)</td>
</tr>
<tr>
<td>TMR maize silage/grass hay/straw</td>
<td>Basal diet maize stalk 23.5% 0 ml 267 mL</td>
<td>Super ovulated heifers with AI and embryo collection cross-over</td>
<td>20 treatment over 10d during superovulation and AI period</td>
<td>1 ↑ 1 ↓ 1 ↓</td>
<td>No difference in growth rate</td>
<td>Number of transferable embryos → number of degenerated embryos → number of unfertilized oocytes recovered →</td>
<td>(63)</td>
<td></td>
</tr>
</tbody>
</table>

TMR total mixed ration, PP: post-partum, ICO: interval calving oestrus, ICAI: interval calving artificial insemination, ICF: interval calving fertilization, DIM: days in milk, P4: progesterone concentrations, CR: conception rate, #: intensive blood sampling after MPG treatment, AMH: anti-Müllerian hormone, ↑: increase, ↓: decrease, -: not measured, %: basal diet starch % not indicated in publication.
| Starch | Amount of starch | Total 
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>50% grass/silage</td>
<td>10.4%</td>
</tr>
<tr>
<td>15%</td>
<td>15% grass/herbage</td>
<td>4.2%</td>
</tr>
<tr>
<td>20%</td>
<td>20% grass/silage</td>
<td>8.7%</td>
</tr>
<tr>
<td>3.5%</td>
<td>3.5% grass/herbage</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Table 3. Summary results of the effect of a dietary glucogenic supplement in the form of starch on reproductive function in non-grazing post-partum dairy cows.**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Source of starch</th>
<th>Duration of study (days)</th>
<th>No. Cows</th>
<th>Treatment</th>
<th>Effect on sup. parameters</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>Grass/silage</td>
<td>35-36</td>
<td>42-44</td>
<td>44</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td>Grass/herbage</td>
<td>35-36</td>
<td>42-44</td>
<td>44</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>Grass/silage</td>
<td>35-36</td>
<td>42-44</td>
<td>44</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>3.5%</td>
<td>Grass/herbage</td>
<td>35-36</td>
<td>42-44</td>
<td>44</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

**Materials and Methods:**
- **Dietary Starch Supplementation:**
  - **Grass/Silage:** 50%, 15%, 20%
  - **Grass/Herbage:** 3.5%

**Results:**
- **Increased:**
  - Total yield, milk production
- **Decreased:**
  - FSH, LH, FSH/LH ratio

**Conclusion:**
- Dietary supplementation with starch significantly improved reproductive function in post-partum dairy cows.

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**References:**
- [97]
- [98]
- [99]
- [100]
3.2. Ovarian activity

3.2.1. Delayed resumption of ovarian cyclicity

Numerous growth factors (insulin and IGF1) and metabolites (glucose) influence gonadotropin-releasing hormone (GnRH) release from hypothalamic neurons [34] and both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are released from the anterior pituitary in response to GnRH [35]. FSH stimulates follicle recruitment and early follicle growth while pulsatile LH is required for continued growth and the development of the dominant ovulatory follicle. Butler [5] found that NEB is strongly associated with low levels of blood glucose, insulin and IGF1 and at the same time LH pulse frequency is reduced. Glucogenic precursors (starch supplement) did not influence FSH concentrations in non-grazing cows [4] and Butler et al. [36] showed that MPG in non-grazing cows had no effect on LH secretion characteristics. To our knowledge only one publication showed a positive effect of MPG on LH pulse frequency [37] and it was in grazing cows. Therefore, glucogenic precursors do not appear to modify FSH and LH secretion parameters. However, the pulsatile nature of their secretion may make studies difficult to undertake.

Britt [38] suggested that the negative effect of NEB on fertility could be explained by a carry-over effect of some metabolites on follicles during their development from inactive primordial follicles up to ovulation which takes between 60 to 80 days. Exogenous and endogenous lipogenic metabolites are acetate, butyrate and long-chain FA while glucogenic metabolites are propionate and starch. A glucogenic diet given between calving and 50 days PP increased plasma insulin and IGF1 compared with a lipogenic diet and this resulted in a greater proportion of cows ovulating by 50 days PP [4]. Rumen MPG fermentation produces propionate and MPG drenches modify ovarian activity and hormones and metabolites [25]. Indeed, ovarian cycles started earlier in cows given MPG drenches PP compared with controls (38% acyclic vs. 58% acyclic at 90d PP) and IGF1 and cholesterol were higher while NEFA was lower although insulin was unaffected [39]. Butler et al. [36] were however unable to show an effect of MPG drenches on ovarian activity in the calving to 27d PP period. Other groups using grazing cows have also been unable to confirm the positive effect of MPG on reproduction [40].

Insulin stimulates follicle recruitment [41] as well as follicular growth and differentiation [42]. Moreover, insulin stimulates in vitro proliferation and function of granulosa [43] and thecal cells [44]. Starch addition to the diet of lactating dairy cows increased insulin concentrations [45] and increased insulin in follicular fluid of preovulatory follicles in high producing dairy cattle [46].

3.2.2. Steroid production

A short luteal phase is often observed during the first oestrus cycle PP. This short luteal phase was prevented by giving MPG drenches which increased insulin and restored normal progesterone (P4) concentrations [25]. In addition, P4 is necessary for the uterine secretion of nutrients and growth factors that are essential for early embryonic development.

Circulating steroid hormone concentrations are affected by their rate of production and clearance (hepatic blood flow and catabolic enzyme activities). In goats, weekly administration of insulin prior to and during gestation increased circulating P4 [47]. Insulin may increase P4 production by stimulating cholesterol uptake across the ovary since there was a strong correlation between glucose and cholesterol uptake by the ovary in ruminants [48].

Moriel et al. [49] showed in ovarioctomized cows given a P4 intra-vaginal implant that when dietary treatment increased insulin, P4 concentrations were also higher. P4 is inactivated in the liver by cytochrome P450 2 C (CYP2 C) or cytochrome P450 3A (CYP3A) [50,51]. Elevated insulin concentrations produced by dietary manipulation (high starch vs. high fibre) decreased P4 clearance and prolonged P4 half-life in lactating dairy cows [52] without any changes in liver blood flow. CYP2 C activity was decreased and CYP2 C mRNA expression tended to be decreased, and CYP3A activity tended to be reduced and CYP3A mRNA expression was unaffected (starch vs. fibre [53]). Finally, Lemley et al. [54] demonstrated that MPG or insulin infusion decreased the abundance in liver biopsies of mRNA for enzymes responsible for hepatic P4 catabolism. In conclusion, insulin appears to increase circulating P4 concentrations by increasing cholesterol uptake by the ovary and by reducing hepatic steroid clearance.
3.3. Oestrus expression

High producing cows have shorter oestrous periods and lower plasma oestradiol (E2) concentrations than those producing less milk [55]. These observations are partly explained by an increase in hepatic clearance since high milk production is associated with high feed intake [56]. In vivo Butler et al. [57] using a hyperinsulinaemic-euglycemic clamp in PP dairy cows showed that NEFA decreased and, IGF1 and E2 increased. Further experiments have also confirmed the positive effect of insulin on E2 production in superovulated goats [58]. Therefore, insulin appears to have positive effects on E2 production and may improve the expression of oestrous.

3.4. Pregnancy rate

Although insulin has positive effects on follicle growth, it is important to reduce insulin levels during the insemination period. Indeed, high insulin induced by high starch diets during the insemination period had negative effects on oocyte quality and blastocyst development rate [59] and pregnancy rate tended to be reduced [60]. Gamarra et al. [61] showed that MPG drenches during superovulation in heifers improved the production of grade 1 oocytes, expanded blastocysts and embryos after ovum pick-up (OPU), in vitro maturation (IVM), fertilization and culture. The collected oocytes were no longer under the influence of high insulin during fertilization and culture since they had been collected and placed in culture medium. Recently using a similar model, Dupras et al. [62] showed that MPG during superovulation and up to the first 4d after artificial insemination (AI) did not influence the number of transferable embryos collected 6d after AI. This finding supports the conclusions of Fouladi-Nashta et al. [59] and Garnsworthy et al. [60].

In conclusion, increasing glucogenic nutrients in the early PP cow could stimulate follicle growth (via increased glucose, insulin and IGF1), limit lipolysis and ceramide production (via insulin) and support P4 concentrations.

3.5. Inconsistencies in results

Not all experiments have shown a positive effect of glucogenic precursors on reproductive success. Several factors are identified to explain these discrepancies (Tables 1–3): sampling frequency, type of feeding system, the genetic background of the cows and a lot of the studies were under-powered. Infrequent sampling (weekly) often resulted in no visible effect of the glucogenic supplement on circulating hormones and metabolites while frequent sampling did. The feeding system modifies the glucogenic profile of the basal diets. Grazing would provide a more lipogenic profile (high sugar and fibre levels) compared with conserved forages (maize silage). Lastly, the genetic background of the cows was different in the studies: New Zealand Holstein and Jersey-Holstein crosses compared with North American Holstein cows. The latter have been shown to produce more milk and mobilize more body reserves. Part of the effect of an increase in milk production was attributed to a reduction in insulin sensitivity in North American cows compared with New Zealand cows [63].

4. Practical suggestions to manipulate insulin concentrations

4.1. Limit ketosis and steatosis

It has recently been estimated that the average cost of a case of clinical ketosis and a case of sub-clinical ketosis were respectively, €709 and €150 [64]. Monopropylene glycol was first reported to be useful in the treatment of ketosis in the 1950’s [65]. McArt et al. [66] showed that oral drenching with MPG decreased hyperketonaemia in early lactation dairy cows. While Rukkwamsuk et al. [67] showed that drenching with 400 mL MPG once daily from 7 days prior to expected calving until 7 days after calving reduced steatosis. Therefore, cows with a higher body condition score (BCS) than recommended prior to calving (≥3.5 on a 5 point scale) could be given (−1 to +2 weeks) MPG daily (300 mL/cow/d [66],) either mixed with the concentrates of the diet or given as a drench. MPG will limit adipose tissue lipolysis and steatosis by stimulating insulin secretion and promoting NEFA catabolism.

4.2. Encourage ovarian cyclic activity

The idea is to “kick-start” normal ovarian activity in the period +2 to +8 weeks prior to insemination to improve conception rate [68].

Firstly, increase dietary starch level. High rumen fermentable dietary starch is one of the risk factors for acidosis. Maize and sorghum are high in “rumen protected” starch compared with wheat [195–215 g/kg DM vs. 65 g/kg DM [69]. Sauvant et al. [70] calculated that there was no risk of acidosis if dietary rumen digestible starch was below 25% of dry matter. Climate change, currently characterized by increased atmospheric CO2, rising temperatures and above all an alteration in the pattern of precipitation [71], may mean that growing sorghum is easier than maize to provide starch since sorghum is much more resilient to low rainfall than maize [72]. In addition to the choice of grain type, the preparation method [73] as well as maturity of grain at harvest are important [74]. Mature ground or rolled grain is recommended [75]. Rumen resistant starch may not be completely hydrolysed in the small intestine [76] due to starch increasing small intestine viscosity
Therefore, the total starch level of the diet should be lower than 35–40% to avoid acidosis and allow complete starch hydrolysis [77]. To ensure complete hydrolysis the quantity of starch reaching the small intestine should not exceed $=2.5$ kg/d [76]. Secondly MPG could be added to the diet. MPG does not cause acidosis. However, MPG is relatively un-palatable and may reduce feed intake if top-dressed on forage. The time course of MPG action is probably different from starch because its effects on glucose and insulin are relatively short-lived, 2–3 h, and of large amplitude. MPG can either be given as a drench or mixed with a concentrate in an automatic concentrate feeder such as in robotic milking systems. In conclusion, a supplement of $\approx 300$ mL MPG/cow/d [66] can be given to stimulate reproductive function. Nielsen and Ingvarsten [65] concluded in their review that at levels of supplementation below 500 g/d unwanted side-effects should not be observed although individual cow responses were variable.

5. Conclusion

Glucogenic treatments have a dual role in the improvement of reproductive success. Firstly, through effects on metabolism and secondly, through direct effects on reproductive function.

Glucogenic treatments affect metabolism by reducing the risk of ketosis and steatosis by decreasing lipomobilisation and stimulating ketone oxidation. Limiting lipomobilisation reduces circulating palmitic acid and ceramide production. The latter can cause insulin-resistance and reduce the availability of glucose for the ovary therefore limiting ovarian function.

Glucogenic precursors appear to affect reproductive function by a local (ovary) rather than central mechanisms since they do not influence FSH and LH secretory characteristics. At the local level glucogenic precursors increase follicle recruitment, growth and differentiation, increase E2 concentrations (through improved granulosa and theca cell proliferation and function) and P4 concentrations (increased secretion by the corpus luteum and reduced clearance by the liver) and generally improve oocyte quality. However, maintaining high insulin around insemination may decrease oocyte quality and embryo survival.

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Disclosure statement

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