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Review

Galactogogues and breastfeeding

Focus on new natural solutions for hypogalactia

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Breastfeeding: benefits to mothers and newborns

Maternal milk is still considered the optimal feeding for all babies till 1 year of age, because it is a species-specific nourishment for the baby and has a direct impact on growth, development and health in the neonatal period; furthermore, it supports a good mother–baby relationship [1–3]. It has been clearly demonstrated that preterm infants receiving maternal milk have better outcomes, both nutritional (supply of polyunsaturated fat acids and proteins) and non-nutritional (reduced incidence of infections and atopic eczema) [4, 5]. Due to the extensive evidence of the long-term benefits of breastfeeding for infants and mothers, in 2003 the World Health Organization (WHO) recommended infants be exclusively fed with breast milk until 6 months of age [6].

A larger population study, evaluating 92,364 newborns, 56,865 (61.6%) of whom were exclusively breastfed at discharge, showed that older, non-smoking, higher-income mothers with no pregnancy complications or reproductive assistance, mothers cared for by midwives and general practitioners and women with spontaneous vaginal birth were more likely to breastfeed. On the contrary, mothers of twins, women who did not attend prenatal classes, with planned or unplanned caesarean delivery and mothers of preterm infants were less likely to exclusively breastfeed; in addition, birth in a baby-friendly hospital is associated with long breastfeeding [7].

The issue of hypogalactia

Reduced breast milk production (also known as hypogalactia), which is the most frequent cause of breastfeeding failure, can occur after a preterm birth, illness of the mother or child, mother–baby separation, re-lactation after a prolonged suspension, indirect lactation (breast pump or manual milk expression), or episodes of anxiety, fatigue and/or emotional stress [1].

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Furthermore, the perception of reduced breast milk production is one of the main reasons for medical consultation in the first months of a baby's life [1, 8].

Physicians need to provide information regarding best practices for breastfeeding and, if necessary, they should indicate methods to support breast milk production, for example the use of galactogogue medications to support breast milk production, ensuring that these problems do not lead to cessation of breastfeeding.

As shown in the Infant Feeding Practices Study II (IFPSII) longitudinal study, continued professional support may be necessary to address mothers and help them to meet their desired breastfeeding duration [8]. The study evaluated the prevalence and factors associated with not meeting desired breastfeeding duration in 1177 mothers aged ≥18 years who responded monthly to several questions about their pregnancy up to one year later. The most important finding was that approximately 60% of mothers stopped breastfeeding earlier than desired, with a mean breastfeeding duration of only 3.8 months. In particular, the lack of enough milk, considered as a nutritional factor, was reported by 57.8% of mothers who did not meet their desired breastfeeding duration versus 29.9% of those satisfied with the duration ($p<0.0001$). Also, early termination was positively associated with mothers' concerns regarding difficulties with lactation, infant nutrition and weight, illness, the need to take medicine and the effort associated with pumping milk [8].

The correlation between stress and hypogalactia

Birth is a stressful event and there are significant changes in the hormonal profile associated with parturition, particularly in the stress-related hormones. Chen et al. demonstrated that primiparity, long labour, stress during labour and delivery and elevated cord glucose are risk factors for delayed lactogenesis. In particular, they found a significant correlation between delay of breast fullness, delay of casein appearance, low levels of milk lactose concentration on day 5 and higher levels of cortisol, one of the most important stress hormones [9]. The influence of stress on plasma oxytocin and prolactin (the hormone essential for the lactation) concentrations on milk production was evaluated in 18 mothers of preterm infants. The results showed that median milk production of these women was similar to that of breastfeeding mothers, but a third produced less than half as much by week 6. Prolactin concentration (AUC) declined during weeks 2–6 postpartum ($p=0.03$); a significant increase of plasma PRL occurred after pumping at weeks 2 and 4, but not at week 6. The Authors concluded that a deficit of preterm lactation can be partially mediated by the stress-induced suppression of prolactin secretion through an adrenergic mechanism [10].

Galactogogues

Galactogogues are synthetic or plant molecules able to induce, maintain and increase milk production, both in women and in dairy animals [3, 11]. The use of these substances should be reserved for cases of primary reduced milk production, without any recognised and treatable cause, and for surrogate or adoptive mothers [1].

Pharmacological galactogogues

The most common pharmacological galactogogues for human use are the dopamine antagonists (metoclopramide, domperidone, chlorpromazine and sulpiride). These drugs block the dopamine 2 receptors (D2R) at the central nervous system (CNS) level, inducing an increase of prolactin synthesis in lactotrophic cells of the anterior pituitary. As a consequence, the high plasma concentration of prolactin increases milk production as well as the proliferation of mammary epithelial cells [3]. Unfortunately, these drugs have important side effects both in mothers and in infants, especially at the CNS level. Gastrointestinal disorders, headache, xerostomia, cardiac arrhythmia, insomnia, depression,

seizures, lethargy, sedation, extrapyramidal symptoms, facial seborrhea, hyperhidrosis and even sudden death have been observed in mothers treated with dopamine antagonists as galactogogues. Episodes of intestinal discomfort, lethargy and sedation were reported in infants receiving milk from treated mothers [1, 3]. Other drugs with galactogogic properties are oxytocin (contraction of the myoepithelial cells that surround the alveoli and milk ducts, causing milk ejection; no adverse events), growth hormones (GH; somatotropin, mechanism of action not yet completely known, no adverse events), thyrotrophin-releasing hormone (TRH; stimulation of the secretion of thyroid-stimulating hormone and prolactin by the pituitary gland; some cases of iatrogenic hyperthyroidism and diaphoresis in mothers) and medroxyprogesterone (mechanism of action unknown, no adverse events except amenorrhea) [1, 3].

Natural galactogogues

Plants with galactogogue properties include fenugreek (*Trigonella graecum foecum*), fennel (*Foeniculum vulgare*), Goat's Rue (*Galega officinalis*), asparagus (*Asparagus racemosus*), anise (*Pimpinella anisum*), milk thistle (*Silybum marianum*) and others (basil, mauve, verbena, cumin, grape and coffee). The galactogogue effects of plants could be mediated by a phytoestrogen action: in fact, some molecules may have effects similar to 17 beta-estradiol, which may induce prolactin expression in anterior pituitary lactotroph cells and promote the proliferation of mammary epithelial cells [3, 12]. However, this is an assumption because for most natural products no scientific studies are available that have demonstrated this effect.

The most frequently used natural galactogogue products include Galega and silymarin [1].

Galega officinalis (Goat's Rue) is a herbaceous plant originating in central and southern Europe. Its lactogenic property in terms of increased milk production and lactation persistency has been demonstrated in animals [3]. Several phytoestrogens have been isolated from methanol extracts of Goat's Rue, such as flavonol triglycosides, kaempferol and quercetin [13].

Silymarin is the active compound of milk thistle (*Silybum marianum*, a member of the Carduus marianum family indigenous to Kashmir, North America, Canada and Mexico), made up of a mixture of four flavonolignans: silybin A and B (60–70%), silychristin (20%), silydianin (10%) and isosilybin (5%) [1, 3, 14]. The flavonolignans are bioflavonoid phytoestrogens, steroid-like molecules which could stimulate the oestrogen receptors limiting the endogenous receptors' antagonism of milk production [1]. Thanks to its composition, silymarin has been reported to have a galactogogue effect [11].

Phytotherapic products are medicines whose active ingredient is derived from plants with a good safety profile. The increasing use of herbal extracts in Europe and Italy, including natural galactogogues, can be explained by factors such as worries about the adverse effects of synthetic drugs, increasing knowledge of the chemistry, pharmacology and clinical use of herbal extracts, the development of analytical methods for increasing quality control and modern methods of industrial production and administration [3]. A problem of many herbal extracts is the poor lipid solubility or improper molecular size, resulting in reduced absorption due to the inability to cross the lipid membranes of the intestines and low bioavailability, despite a well established *in vitro* activity. Currently, the bioavailability of herbal extracts can be improved with the use of different novel delivery systems like liposomes and phytosomes, which can enhance the ability to cross the lipid-rich biomembranes [15].

Innovative delivery systems for phytotherapics

Herbal extracts are characterised by low solubility and poor bioavailability. In order to increase their absorption and therefore their efficacy, a new formulation was developed and used as a delivery system: a phytosome composed of silymarin and phospholipids (phosphatidylserine). Phosphatidylserine

acts as a carrier for insoluble molecules, enhancing their intestinal absorption. Thanks to its lipid structure, phosphatidylserine can integrate into the cellular lipid barrier, delivering the active ingredient directly into the cell and improving its bioavailability. This new formulation has several important advantages over conventional formulations of plants and extracts: improvement of solubility and bioavailability, protection from toxicity, enhancement of pharmacological activity and stability, improved tissue macrophage distribution, sustained delivery and protection from physical and chemical degradation [16]. In addition, phosphatidylserine has antioxidant effects and regulates cortisol levels [17, 18].

The phytosome containing silymarin, named Silitidil®, is able to clearly improve the bioavailability of sylmarin in comparison with normal (pure) silymarin and micronised silymarin (BIO-C) (Fig. 1) (data on file).

A recently published pharmacological study from Capasso et al. evaluated the effect of Silitidil (silymarin–phosphatidylserine) and the association Silitidil plus *G. officinalis* on prolactin blood levels in comparison with control and Silymarin BIO-C in mature female Wistar rats [19].

The study included three dose series of tests. In the first series of experiments, rats were treated daily for 14 days with water (0.3 ml/rat) and Silitidil/Galega (25–200 mg/kg orally). In the second series of experiments, rats were treated daily for 14 days with water (0.3 ml/rat), Galega (200 mg/kg per os), Silitidil (50–100 mg/kg per os) and Silitidil/Galega (50–100 mg/kg per os). Finally, in the third series of experiments, rats were treated daily with water (0.3 ml/rat), Silitidil/Galega (200 mg/kg per os), bromocriptine (1.0 mg/kg ip) and bromocriptine (1.0 mg/kg ip)+Silitidil/Galega (200 mg/kg per os). After treatment, rats were anaesthetised to determine blood prolactin levels.

The results showed that the administration of Silitidil (25–200 mg/kg per os) was able to increase serum prolactin levels in rats in a dose dependent manner. Interesting, the prolactin induction was

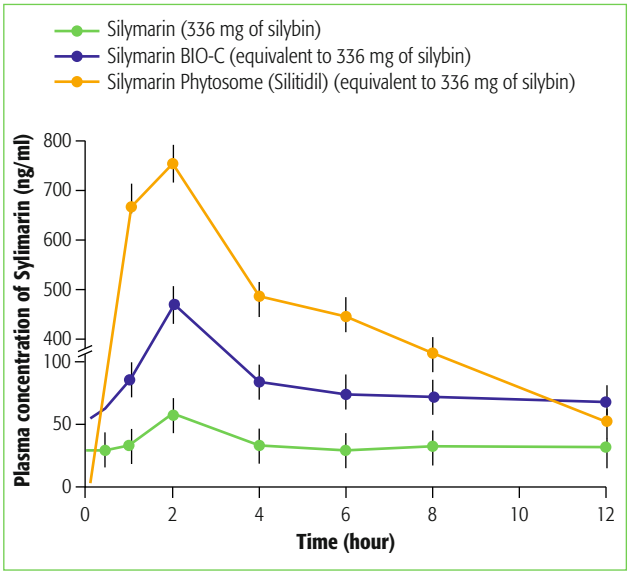

Figure 1 Plasma concentration of Silitidil, micronised silymarin (BIO-C) and pure silymarin

superior when female rats were treated with Silitidil® in comparison with the micronised Silymarin (BIO-C) (Fig. 2). Bromocriptine significantly reduced the high serum prolactin levels induced by Silitidil (200 mg/kg per os) [19].

In addition to the *in vitro* and *in vivo* (rats) data on the galactogogue activity of milk thistle, few studies in humans are available. Di Pierro et al. evaluated the clinical efficacy, safety and tolerability of micronised silymarin (BIO-C) as a galactogogue in 50 healthy women during breastfeeding [20]. The women received oral treatment with micronised silymarin (BIO-C) (420 mg/day, n=25) in comparison with a placebo product (n=25) for 63 days. The quantity of produced milk was measured on days 0, 30 and 63; in addition, milk samples were collected for a qualitative profile. The study results clearly demonstrated the galactogogue activity of micronised silymarin: in fact an increase in daily milk production equal to 85.94% was observed in the treated group versus 32.09% in the placebo group. The safety profile and compliance were good: no drop outs or adverse effects were reported in either group. The Author stated that silymarin can safely and effectively improve daily milk pro-

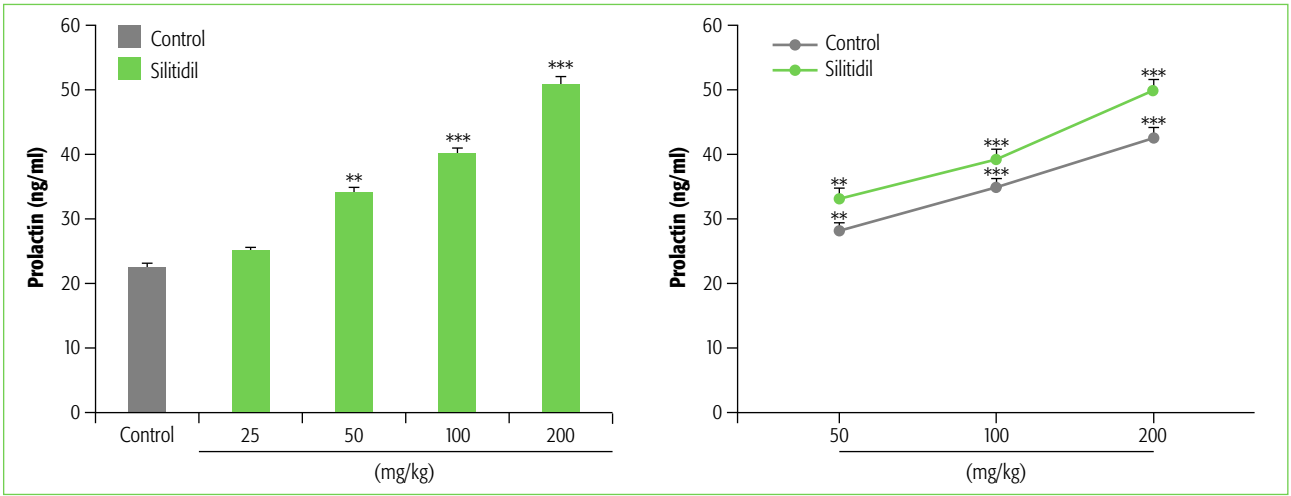

Figure 2 Plasma prolactin concentrations after administration of Silitidil, micronised silymarin (BIO-C) and control (modified from [19])

duction in healthy women after delivery, without affecting milk quality [20].

A recent observational study compared the effect on breast milk production of an oral maternal supplementation of two galactogogues (silymarin plus Galega) in term (n=16) and preterm (n=16) mothers (preterm infants recovered in a neonatal intensive care unit). The results showed that at baseline the milk production was reduced in preterm mothers versus term mothers (p<0.08), but after the treatment with the combination of silymarin a plus Galega, the milk production was similar in both groups within 2 months [21].

In conclusion, reduced breast milk production represents a real problem in around two thirds of lactating women. Even though pharmacological options are currently available for inducing, maintaining and increasing milk production, mothers prefer natural remedies, such as herbal extracts. Silymarin, the active compound of milk thistle, has been demonstrated to have several therapeutical and physiological activities, including a galactogogue effect, but its intestinal absorption is poor, as for most herbal extracts. A new phytosomal formulation of silymarin has been shown to improve both bioavailability and prolactin plasma levels in comparison with older formulations of silymarin. Based on available data, this formulation could be considered a safe and effective natural product able to improve daily milk production in healthy women after delivery, without affecting milk quality.

Conflict of interest

The authors declare that there is no conflict of interest.

Human and Animal Rights

The article does not contain any studies with human or animal subjects performed by any of the authors.

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