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ORIGINAL ARTICLE

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Canine and feline colostrum

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Puppy and kitten survival over the first weeks is particularly dependent on colostrum, a specific secretion of the mammary gland produced during the first 2 days post-partum. Colostrum is a source of nutrients and immunoglobulins. It also contributes to the digestive tract maturation. Colostrum differentiates from milk mainly based on its concentration in immunoglobulins G: 20–30 g/L in dog colostrum, 40–50 g/L in cats' vs <1 g/L in milk. IgG concentration rapidly drops after parturition (−50% in 24 hr). Immune quality of colostrum is highly variable between bitches, with no relationship with maternal blood IgG level, dam's age, breed size or litter size. In addition to systemic immune protection, colostrum also plays a major role for local digestive protection, due to IgA, lysozyme, lactoferrin, white blood cells and various cytokines. Energetic concentration of canine and feline colostrum is not superior to that of mature milk. It depends on colostrum fat concentration and is affected by breed size (higher in breeds <10 kg adult body weight). As puppies and kittens are almost agammaglobulinemic at birth, transfer of IgG from their digestive tract into their bloodstream is crucial for their survival, IgG absorption ending at 12–16 hr after birth. Energetic supply over the two first days of life, as evidenced by growth rate over the two first days of life, also affects risk of neonatal mortality. Early and sufficient suckling of colostrum is thus the very first care to be provided to newborns for their later health and survival.

1 | INTRODUCTION

The neonatal period (from birth to 21 days of life) is a major risk period for feline and canine newborns as approximately 20% of live-born puppies and kitten die before they are 21 days old; 70–90% of deaths occur during the first week post-partum (Fournier et al., 2016; Gill, 2001; Mila, Feugier, Grellet, & Chastant-Maillard, 2015a). In carnivores, survival of newborns within the first 3 weeks of life is particularly dependent on colostrum, a specific secretion of the mammary gland produced during the first 2 days post-partum. Colostrum is crucial for newborns as it provides them with nutrients and immunoglobulins. In puppies, both the quality of passive immune transfer (evaluated by circulating IgG levels at 2 days of age) and the energy ingested (as evaluated via the growth between birth and 2 days of age) have been demonstrated to control the risk of neonatal mortality (Mila, Grellet, Feugier, & Chastant-Maillard, 2015b; Mila et al., 2014). The following article reviews recent findings concerning canine and feline colostrum, and the role for puppies' survival and development.

2 | IMMUNE ROLE OF COLOSTRUM

2.1 | Immunoglobulins

In carnivores, colostrum distinguishes from milk by a markedly higher concentration in immunoglobulin G (IgG): 20–30 g/L in dog colostrum, 50–70 g/L in cats' vs <1–5 g/L in milk (Claus, Levy, Macdonald, Tucker, & Crawford, 2006; Schäfer-Somi, Bär-Schadler, & Aurich, 2005). IgG from the dam's bloodstream is trapped into the mammary cells during the last weeks of pregnancy by their fixation on specific receptors (FcRn, fragment constant receptor neonatal). They thus accumulate into the mammary tissue at the end of pregnancy. At parturition, IgG

is massively released into the first mammary secretions, with colostral levels typically 3–4 times higher than in the maternal bloodstream (Claus et al., 2006; Mila et al., 2015c). Nevertheless, IgG rapidly drops from parturition, with a reduction of 50% over the first 24 hr; at day 7, IgG has fallen to ~5 g/L and to <1 g/L on day 14 (Albaret, Mila, Grellet, & Chastant-Maillard, 2016; Claus et al., 2006; Schäfer-Somi et al., 2005). This dramatic reduction is explained by the translocation of the FcRn receptor at parturition from the basal to the apical aspect of glandular cells (Kuo et al., 2010), allowing IgG from secretions to be recaptured through the maternal bloodstream. This IgG after parturition allows to set the transition from colostrum to milk at the third day post-partum.

Other immune difference between colostrum and milk is the proportion of the different classes of immunoglobulins. In colostrum, class G is the dominant one. Proportions in the canine colostrum are 60% IgG, 35%–40% IgA and 5% IgM, IgE being undetectable. In the feline colostrum, 96% of immunoglobulins are IgG, vs 2% of IgM and 2% of IgA (Casal, Jezyk, & Giger, 1996). Whereas IgG originates mainly from the maternal bloodstream, IgA and M are rather produced locally in the mammary tissue. In milk, IgA becomes the dominant type (90% of Ig), IgG and IgM accounting both for only 5% (Chastant-Maillard et al., 2010; Schäfer-Somi et al., 2005).

Colostral Ig is of crucial importance for puppies and kittens survival, both for systemic (IgG) and local (IgG and IgA) immunity. Due to the endotheliochorial structure of their placenta, these newborns are nearly agammaglobulinemic at birth: IgG in the newborn's blood at birth is approximately 0.3 g/L to be compared to 8–25 g/L in adult dogs (Bouchard et al., 1992; Poffenbarger, Olson, Chandler, Seim, & Varman, 1991), respectively, 0.1 vs 15–20 g/L in cat (Casal et al., 1996; Levy, Crawford, Collante, & Papich, 2001). Ingested colostral IgG is absorbed from the gut lumen into the intestinal lymphatic vessels and then to the newborn's bloodstream either by specific or non-specific transfer: specific transport depends on FcRn receptors, also expressed by enterocytes, whereas Ig also crosses freely the digestive epithelium between the loosely associated enterocytes. Interestingly, colostrum is also highly concentrated in antitrypsins (1,000-fold higher than in milk; Levieux & Ollier, 1999), protecting Ig from digestive processes. Nevertheless, digestive wall differentiation, beginning as early as birth, restricts Ig absorption to a short window of time after birth: development of the brush border and establishment of tight junctions between enterocytes progressively limit IgG intestinal crossing. At birth, in puppies, 40% of the ingested Ig is absorbed from the gut lumen through the bloodstream, whereas only 20% at 4 hr after life; from 12 to 16 hr after birth, intestinal barrier is totally closed, both in puppies (Chastant-Maillard et al., 2012) and in kittens (Casal et al., 1996). From above, an early suckling appears necessary for an adequate acquisition of passive immunity, first due to the rapid decrease in colostral [Ig] in the first hours post-partum and secondly to the timing of the intestinal barrier closure.

From nearly null at birth, IgG is maximal in the newborns' blood thanks to colostral intake at 24–48 hr after ingesting colostrum. At that stage, puppy's blood IgG will be in the order of 6, 25 g/L in kittens, 85%–97% of circulating Ig being of colostral origin (Casal et al., 1996; Chastant-Maillard et al., 2012; Levy et al., 2001). The threshold defining deficit in passive immune transfer has been determined in puppies at 2.3 g IgG/L serum at 2 days of age (Mila et al., 2014): neonatal mortality rate (from birth to day 21) is 44% for puppies whose concentration is below the threshold vs 4.9% for those above. The minimal IgG protective for kittens is lacking to date. IgA is also absorbed before intestinal barrier closure, but it is rapidly resecreted through mucosa, especially respiratory and digestive, where it plays a role in local immunity (Chastant-Maillard et al., 2012; Salmon, Berri, Gerdts, & Meurens, 2009).

But intestinal barrier closure does not end the immune role of colostrum. Ingested immunoglobulins, both IgG and IgA, enclosed into the digestive lumen, participate in digestive local immunity, either by trapping pathogens or by contributing to antigen presentation to white blood cells.

2.2 | Other immune factors

Colostrum provides other components with an immune role: non-specific antibacterial factors such as lactoferrin and lysozyme, together with cytokines, involved in immune response and white blood cell activation. Colostrum also contains white blood cells, (macrophages, neutrophils and lymphocytes): these cells are absorbed by the newborn before the intestinal barrier closes and either enter the circulation or play a role in cellular, humoral or local digestive immunity. Colostral mucin, lactadherin and oligosaccharides also prevent the adhesion of pathogens to enterocytes (Stelwagen, Carpenter, Haigh, Hodgkinson, & Wheeler, 2009).

Colostrum will also indirectly contribute to the defence of the organism against pathogens by promoting intestinal barrier closure, initiated by colostral hormones (especially insulin and cortisol), and enterocytes become more closely associated, limiting the penetration of pathogens from the digestive tract into the newborn's bloodstream.

2.3 | Improving the immune quality of colostrum

The immunological quality of the colostrum, in terms of IgG concentration, is quite variable, both between female dogs and between teat pairs of the same female. In one study looking at the colostrum of 44 female dogs of the same breed, the IgG levels varied between females by a factor of 5. The IgG concentration in 180 samples from different teat pairs varied between 0.8 and 61 g/L, with a variation coefficient of 42% between teat pairs of the same bitch (Mila et al., 2015c). However, the teat pair producing the highest-quality colostrum varies from one animal to another, so there is no value in advising puppies should suckle from one particular teat. The variation of IgG between teats is unknown in queens. During the colostral period, neither kittens nor puppies develop a nipple preference (Arteaga, Rödel, Elizalde, Gonzalez, & Hudson, 2013; Hudson, Raihani, Gonzalez, Bautista, & Distel, 2009). Nevertheless, passive immune transfer may markedly differ between puppies of the same litter (Figure 1), probably due to either differences in the quantity, the quality and/or the timing of colostral ingestion.

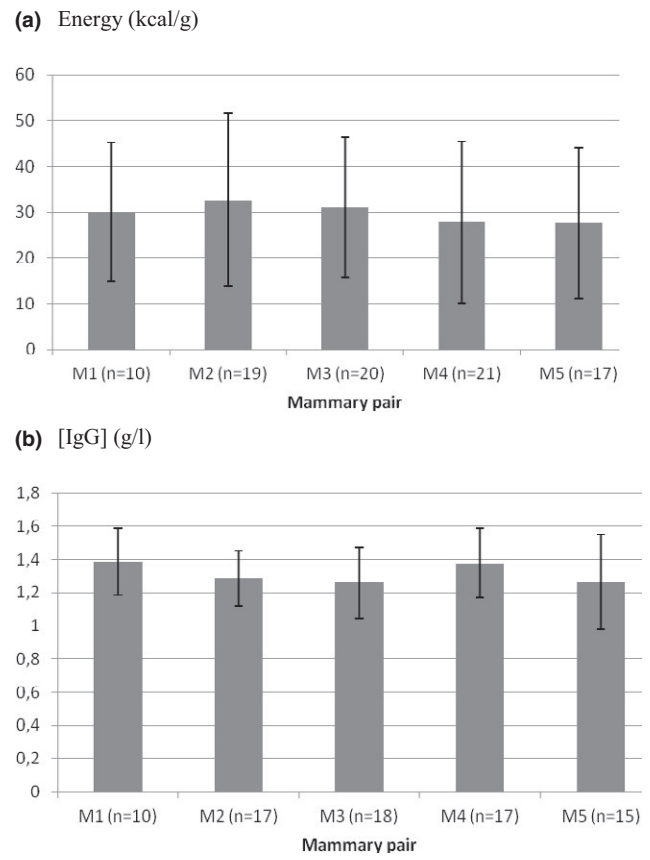

FIGURE 1 Immune (a) and energetic (b) value of canine colostrum depending on mammary pair number. M1: thoracic to M5: inguinal. Mean ± *SD*. Between brackets, number of bitches. $p > .05$ for both criteria

The immune quality of colostrum (as evaluated through colostral IgG) seems to be difficult to be improved. Neither the dam's age, litter size nor breed size influenced colostral IgG (Mila et al., 2015c). Ensuring appropriate nutrition of the dam during gestation and its good general health are basic prerequisite. Despite colostral IgG originate from the maternal bloodstream, no relationship appeared between the colostral IgG and the maternal serum concentration (Chastant-Maillard et al., 2012; Mila et al., 2015c). Moreover, the risk for deficit in passive immune transfer of puppies is not associated with the mean colostrum IgG delivered by the dam (Mila et al., 2014). However, one strategy may be to increase the proportion of antibodies directed against pathogens affecting the newborn, such as the canine parvovirus CPV-2, canine herpesvirus CHV-1 or feline herpes or calicivirus. This specific enrichment can be obtained by vaccination of the dam during the second half of pregnancy and/or at short distance of heats for antigens whose vaccination is contraindicated during pregnancy.

3 | ROLE IN ORGAN MATURATION

As presented above, colostrum contains significant quantities of hormones (cortisol, insulin, thyroxin, growth hormone) and several growth factors (insulin-like growth factors, epidermal growth factor, nerve growth factor) (15). These substances are involved in the development and maturation of several organs, namely the digestive tract, the liver, the pancreas and the thyroid (Heird, Schwarz, & Hansen, 1984). This maturation then improves intestinal absorption of further nutrients and the newborn's metabolism.

4 | NUTRIENTS SUPPLY

Energy is provided in colostrum nearly equally by proteins (50% of colostral energy) and by lipids (40%), but variations in the energy value are principally explained by variations in the lipid levels (Mila et al., 2015d). In carnivores, energy concentration (kcal/ml) is similar in colostrum and in milk, but the pattern during lactation differs slightly between bitch and queen. In dogs, energy value progressively decreases by 20% during the two first weeks post-partum, whereas in queens, it more rapidly drops (−30% over the first 3 days) and then increases progressively over the whole lactation (Adkins, Lepine, & Lonnerdal, 2001; Adkins, Zicker, Lepine, & Lönnerdal, 1997). In comparison with canine (1,300–1,800 kcal/L) and feline colostrum (1,300 kcal/L), energy value of milk replacers ranges between 500 and 1,500 kcal/L (Adkins et al., 1997, 2001; Heinze, Freeman, Martin, Power, & Fascetti, 2014; Mila et al., 2015d).

The energy value of colostrum can vary between dams by a factor of 1.6, which is a fairly small range compared to variations of its immune value; differences between teat pairs of the same dog are also much more limited for energy than for IgG with a variation coefficient of approximately 8%, as opposed to 42% for the immunological value (Mila et al., 2015c). Interestingly, the immunological quality and energy value of colostrum are not correlated (Figure 2; Mila et al., 2015d).

Age and litter size have not been shown to affect the energy value, whereas bitches from small breeds (<10 kg) have colostrum with 10% more energy than females from large breeds (>40 kg) (unpublished data).

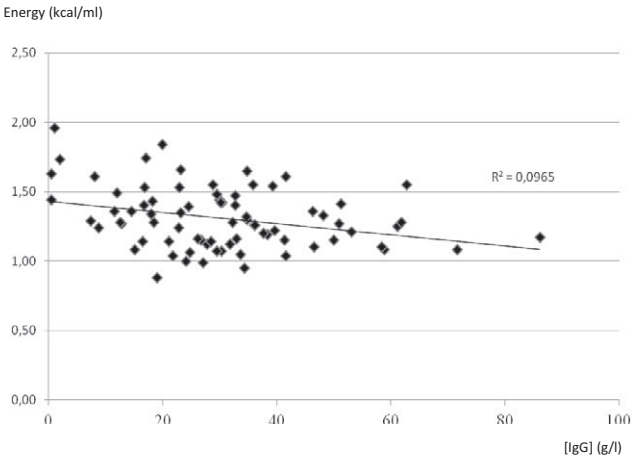

FIGURE 2 Absence of correlation between IgG and energy concentrations in canine colostrum. A total of 77 samples from 21 bitches ($p > .05$)

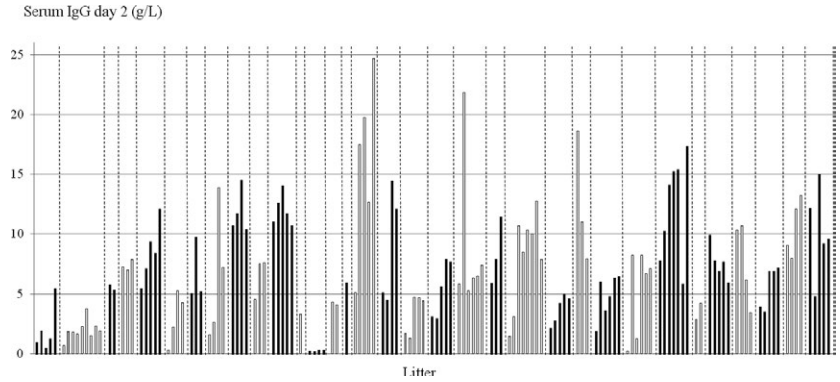

FIGURE 3 Differences in passive immune transfer between litters and between puppies within litters on 34 litters from purebred bitches of various breeds. Each bar represents blood IgG concentration of one puppy; each group of bars of the same colour represents puppies from the same litter

5 | QUALITY VS QUANTITY OF COLOSTRUM

Whilst minimal quality criteria (i.e. threshold levels of colostral IgG and energy concentrations) required to control neonatal mortality have been determined in some species (Tyler, Hancock, Thorne, Gay, & Gay, 1999 in calves; Cabrera, Lin, Campbell, Moeser, & Odle, 2012; in piglets), they are currently unknown for canine and feline. Even the actual quantity of colostrum produced by bitches and queens is unknown, only estimated from milk production measured during the first week post-partum: 2.7% (1%–6%) and 4.1% (1%–8%) of the dam's body weight in bitches and in queens, respectively (Meyers, 1985; on five bitches; Dobenecker, Zottmann, Kienzle, & Zentek, 1998 on six queens). A 10-kg beagle bitch is thus estimated to produce 270 ml of colostrum per day and a 4-kg queen 160 ml of colostrum per day.

Knowledge of the newborns' needs for immunoglobulins and energy allows the calculation of the minimal quantity of colostrum to be ingested. For adequate passive immune transfer (i.e. puppy IgG serum levels of 2.3 g/L), the quantity of average colostrum that must be ingested is 1.3 ml per 100 g of puppy bodyweight within the first 8 hr of life (digestive absorption rate of 40%, 35% haematocrit, colostral IgG levels 20 g/L). In contrast, the average quantity of ingested colostrum required to cover energy needs is much higher, at 12 ml per 100 g of puppy bodyweight per day (energy need of 212 kcal/kg per day if the colostrum supplies 1,800 kcal/l). Similar calculation in kittens shows that the minimal colostral ingestion to cover energy needs is 16 ml per 100 g of kitten bodyweight per day (220 kcal/kg per day; Peterson & Kutzler, 2011). Calculation for sufficient passive immune transfer is impossible to perform due to the unavailability of serum IgG threshold in kittens. Taken together, these results indicate that a beagle dam would be able to produce enough colostrum for eleven 200-g puppies, whereas a standard queen would be able to appropriately nurse ten 100-g kittens. On average, colostral production does not seem to be a major limiting factor for newborns' health. This conclusion is reinforced by the observation of a similar prevalence of immune and energy deficit in puppies (respectively, 20% and 30% at 2 days of age; Mila et al., 2014, 2015b), despite the much higher quality of colostrum required to cover energy needs.

6 | CONCLUSION

Birth induces major physiological changes in the foetus, and the newborn will have to adapt to survive. Among these dramatic changes, the nutrients are no more passively and continuously supplied by the placenta, and the environment becomes hostile, as massively infected by potential pathogens and instable low temperature (vs the sterile, thermoregulated uterus). Colostrum, providing immune factors and nutrients, especially energy, is the key element for a correct adaptation of the newborn to the extra uterine life. In case of its deficit, their survival would depend on an adequate substitute, designed at least to ensure immune and energetic provision.

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CONFLICT OF INTEREST

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. The research from HM cited in this review is funded, at least partly, by Royal Canin Research and Development (Aimargues, France).

AUTHORS' CONTRIBUTIONS

SCM wrote the manuscript and contributed to the design of the protocols and data analysis. CA and AA collected colostrum samples, performed Ig assays and analysed the data. AF provided specific

information on feline colostrum. HM contributed to colostrum sample collection and to the design of the protocols and data analysis and finally revised the manuscript.

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