Postpartum dysgalactia syndrome: A simple change in homeorhesis?

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Summary

Mastitis, metritis, and agalactia syndrome (MMA) is a clear entity often reported as postpartum dysgalactia syndrome (PDS). However, MMA may represent only a small emerging part of an iceberg represented by PDS. Until now, investigators have compiled a list of risk factors for PDS related to nutrition, housing, and management practices and suggested that endotoxins and cytokines may play a central role in development of PDS. However, the pathophysiology of PDS has never been defined. The goal of this paper is to fill this gap, basing our proposal on the most recent published scientific literature and on the concept of homeorhesis developed by Bauman and Currie in the 1980s. Homeorhesis, a term that encompasses dynamic systems that return to a trajectory, refers to orchestrated changes in metabolism of body tissues to prioritize a physiological state (such as gestation or lactation) and brings a new perspective to this multifactorial disease that we will try to clarify using a transdisciplinary approach. Indeed, it appears that the clinical approach to PDS must simultaneously take into account physiology, endocrinology, innate immunology, and ethology.

Keywords: swine; mastitis, metritis, and agalactia syndrome; postpartum dysgalactia syndrome; homeorhesis

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Resumen - El síndrome de disgalactia postparto: un simple cambio en la homeorhesis?

El síndrome de mastitis, metritis, y agalactia (MMA por sus siglas en inglés) es una entidad clara a menudo reportada como síndrome de disgalactia postparto (PDS por sus siglas en inglés). Sin embargo, la MMA puede constituir solamente la punta del iceberg representado por PDS. Hasta ahora, los investigadores han recopilado una lista de factores de riesgo para el PDS relacionados con la nutrición, alojamiento, y prácticas de manejo y sugieren que las endotoxinas y las citocinas pueden jugar un papel central en el desarrollo del PDS. Sin embargo, la patofisiología del PDS nunca ha sido definida. El propósito de este estudio es llenar este vacío, basando nuestra propuesta en la literatura científica recientemente publicada y en el concepto de homeorhesis desarrollado por Bauman y Currie en la década de 1980. Homeorhesis, una palabra que abarca los sistemas dinámicos que retornan a un estado fisiológico (como la gestación o la lactancia) y ofrece una nueva perspectiva a esta enfermedad multifactorial que trataremos de clarificar utilizando un acercamiento multidisciplinario. De hecho, parece que el abordar el PDS clínicamente debe tomarse en cuenta simultáneamente la fisiología, endocrinología, inmunología innata, y la etología.

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Résumé - Syndrome de dysgalactie postpartum: un simple changement de l’homeorhésie?

Le syndrome de mammitis, agalactie, et métrite (MMA) est une entité clinique reconnue qui est souvent rapportée sous l’appellation syndrome de dysgalactie postpartum (PDS). Par contre, le MMA pourrait représenter seulement une petite partie émergente d’un iceberg représenté par le PDS. Jusqu’au récemment, les chercheurs ont compilé une liste des facteurs de risque pour le PDS qui sont reliés à la nutrition, l’hébergement, et les pratiques de gestion et ont suggéré que les endotoxines et les cytokines pourraient jouer un rôle central dans le développement du PDS. Par contre, la pathophysiologie du PDS n’a jamais été définie. L’objectif de cet article est de combler cette lacune, en basant notre proposition sur la littérature scientifique la plus récemment publiée et sur le concept d’homeorhésie développé par Bauman et Currie durant les années 1980. L’homeorhésie est un terme qui englobe les systèmes dynamiques qui reviennent à leur trajectoire, réfère à une cascade de changement dans le métabolisme des tissus visant à prioriser un état physiologique (tel que la gestation ou la lactation) et à amener une nouvelle perspective à cette maladie multifactorielle que nous voulons clarifier en utilisant une approche trans-disciplinaire. En effet, il semble que l’approche clinique envers le PDS peut simultanément prendre en considération la physiologie, l’endocrinologie, l’immunologie innée, et l’ethologie.
Mastitis, metritis, and agalactia syndrome (MMA) is a clear entity\textsuperscript{1} that has been described for at least 50 years.\textsuperscript{2} More recently it has been called postpartum dysgalactia syndrome (PDS).\textsuperscript{3} However, MMA syndrome may be considered the emerging part of an iceberg represented by PDS, which is the more important and underestimated part and therefore the least obvious and most dangerous. In 1982, the name “periparturient hypogalactia syndrome” was proposed\textsuperscript{4} to characterize the disease, and in 1998, it was named “postpartum dysgalactia syndrome” (PDS),\textsuperscript{5} which is now well recognized and accepted in the scientific community.\textsuperscript{3}

Homeorhesis, derived from Greek and standing for “similar flow,” is a concept encompassing dynamic systems which return to a trajectory, as opposed to systems that return to a particular state, defined as homeostasis.\textsuperscript{6} The word “homeorhesis” was proposed by Conrad Waddington (1905-1975), biologist, paleontologist, and embryologist. It refers to “coordinated changes in metabolism of body tissues necessary to support a (dominant) physiological state.”\textsuperscript{7} While well reported in scientific papers,\textsuperscript{7,8} homeorhesis, in contrast to homeostasis, is not very common in the daily swine veterinary language. In the animal science area, homeorhesis is primarily used in connection with cattle production.\textsuperscript{8,9,10}

Taking into account recent scientific information,\textsuperscript{3} we propose that PDS is a consequence of an unsuccessful transition from the homeorhesis of gestation to the homeorhesis of lactation, that we will call a “dys-homeorhesis change.” The transition is very complex and depends on an extensive series of biological adaptations that include many, perhaps most, body tissues and all nutrient classes. Therefore, the pathophysiology of PDS is similar to that of postweaning diarrhea, in which pathology results because of a difficult transition between two completely different diets.\textsuperscript{11}

Postpartum dysgalactia syndrome
Postpartum dysgalactia syndrome is usually investigated using either an infectious or an epidemiological approach. The infectious approach, which starts most commonly with coliform mastitis as the primary event, has been recently well reviewed.\textsuperscript{12} The hypothesis that an infectious agent is at the root of PDS has existed for years and is still current, as shown by the prominence of research trying to isolate and type associated *Escherichia coli* strains, although the hypothesized link between *E. coli* and PDS is not always easy to demonstrate.\textsuperscript{13-15} Epidemiological studies on PDS report findings of two types of observational studies, longitudinal\textsuperscript{16,17} and cross-sectional.\textsuperscript{18} Very recent work conducted in Belgium\textsuperscript{19} identified four major risk factors for PDS: moving the sow to the farrowing stable 4 days before farrowing, rather than > 7 days before, as is common in the commercial swine industry; ad libitum feeding shortly after farrowing; farrowing induction; and supervision of farrowing, as summarized in a table by Maes et al.\textsuperscript{3} Discovery that farrowing induction and farrowing supervision were risk factors for PDS was surprising and unexpected by these authors.

There have been many studies and reports on the infectious component of *E. coli* mastitis. Mastitis is at the heart of the model of PDS that focuses on the acute mastitis paradigm, generating full chapters in books such as *Diseases of Swine*.\textsuperscript{20} In a recent literature review by Gerjets and Kemper,\textsuperscript{21} entitled “Coliform mastitis in sows: a review,” the authors report that clinical mastitis is not as prevalent in sows in Germany as it was in the past. As any temporary decrease in colostrum ingestion causes pathological consequences in the litter, the possible connection between PDS and neonatal diarrhea becomes clear. In 2009 and 2010, we, and Svensmark\textsuperscript{22} in Denmark, reported a new neonatal porcine diarrhea syndrome (NNPD)\textsuperscript{22} that has been frequently reported since then.\textsuperscript{23-26} Neonatal piglet diarrhea has emerged in many European countries (eg, Denmark, Sweden, and France) despite carefully implemented vaccination against enterotoxigenic *E. coli* and good management procedures, taking into account bioscience, hygiene, colostrum intake, nursing, and a high standard of care.\textsuperscript{27} The etiology of NNPD has been unknown until recently, and in most cases microbiological testing is insufficient to explain the cause.

In herds with NNPD, a preliminary study\textsuperscript{28} showed that duration of farrowing is longer in affected herds, and longer in affected than in non-affected litters. Therefore, the pathophysiology of disturbances in farrowing, in litters affected with neonatal diarrhea, has been investigated.\textsuperscript{29-31} The outcome of this work was a surprising correlation: piglets affected with neonatal diarrhea had ingested a high volume of colostrum.\textsuperscript{29} However, Le Dividich et al\textsuperscript{32} observed no diarrhea in neonatal piglets bottle-fed colostrum in amounts up to 561 g per kg body weight per 24 hours. The reason for the observation by Sialleli et al.\textsuperscript{29,30} that diarrheic piglets had consumed a large volume of colostrum, remains to be elucidated.

Homeorhesis
A dys-homeorhesis change is at the heart of PDS (Figure 1). In 1980, Bauman and Currie\textsuperscript{6} reviewed the regulation of nutrient partitioning during pregnancy and lactation. They defined homeorhesis as “the orchestrated or coordinated changes in metabolism of body tissues necessary to support a physiological state.”\textsuperscript{6} The central nervous system coordinates homeorhetic adaptations through the endocrine system. Bauman and Currie\textsuperscript{6} characterized the “key features” of homeorhetic control: its path, ie, hours or days versus seconds or minutes for homeostatic regulation; its simultaneous influence on various and apparently functionally unrelated tissues and systems; and its mediation through altered responses to homeostatic signals.

At farrowing (which may be considered an acute process), the homeorhetic drivers must shift from a pregnancy pattern to a lactation pattern, synchronizing among multiple organs and organ systems the metabolic and hormonal milieu of the sow.\textsuperscript{33} The well-coordinated developmental change in adipose tissue metabolism in late pregnancy is a good example of homeorhesis. Overall, the homeorhetic controls operating during lactogenesis alter adipose tissue metabolism, decreasing lipid synthesis and increasing lipid mobilization, to support a new physiological state. However, homeostatic controls also are operating throughout this period to balance environmental challenges, eg, stress or the daily rhythms in circulating metabolites associated with feeding. The study of Metz and van den Bergh,\textsuperscript{34} focused on these changes in dairy cows at parturition.

During farrowing, huge individual variations in hormonal and biochemical changes are well described.\textsuperscript{35} However, little data indicates how these changes are coordinated. Recent data from studies in rats indicate that changes in mammary, liver, and adipose transcriptomes at the onset of lactation are coordinated through molecular clocks, ie, small molecules acting as metabolic messengers.\textsuperscript{36} These authors suggest principles to explain how molecular clocks might affect
Figure 1: Schematic pathophysiology of postpartum dysgalactia syndrome (PDS) adapted from Martineau et al. Red arrows link risk factors within a box, blue arrows illustrate a connection between boxes, and white arrows illustrate the link between a box and a change of homeorhesis. This material is reproduced with permission of John Wiley and Sons, Inc.
metabolism, on the basis of the review by Michele.\textsuperscript{36} Genes expressed in adipose tissue are believed to regulate both feed intake and whole-body energy metabolism.\textsuperscript{37}

In pregnant sows, a huge acceleration of fetal growth occurs after day 70, but some major changes in fetal composition also occur.\textsuperscript{38} Very accurate data have been obtained in normoprolific gilts. However, one has to take into account that we now have to manage hyperprolific sows, therefore the changes in fetal composition are probably bigger.

### Pathophysiology of PDS

Risk factors for PDS were identified as a result of a large questionnaire survey in commercial pig farms in Belgium.\textsuperscript{19} The aim of the study was to investigate management practices and strategy-related risk factors. On the basis of these results, the same team then proposed a pathophysiological explanation of PDS involving nutrition, housing, and management practices.\textsuperscript{3} The authors do not mention homeorhesis, taking into account the changes occurring physiologically in gestation and lactation metabolisms, related to energy, protein, water, minerals, and anion gap. We believe the unsuccessful change in homeorhesis (ie, the “dys-homeorhesis change”) when shifting from gestation to lactation is at the heart of PDS and propose a novel pathophysiological explanation summarized in Figure 1.

Hormones and their regulation are an essential component of the homeorhesis transition. An example of the complexity of the interactions and feedback loops is shown in Figure 2.\textsuperscript{39} Question marks show the several remaining issues regarding the interactions between reproductive and stress hormones, but it seems appropriate to emphasize that we need “a favorable hormonal milieu” for gestation and for lactation.\textsuperscript{40}

Foisnet et al\textsuperscript{41} demonstrated the consequences of asynchrony between progesterone and prolactin on colostrum production in sows showing no clinical signs. They concluded that sows producing a low yield of colostrum were characterized by a leaky mammary epithelium and reduced synthesis of lactose, related to delayed hormonal change before farrowing. These sows had greater plasma progesterone the day before farrowing, and tended to have lower plasma prolactin levels 1 to 2 days before farrowing, than did sows with a high yield of colostrum. Consequences of poor colostrum production on production parameters (such as average daily weight gain of the piglets) have been reported, as have decreased concentrations of prolactin\textsuperscript{42} and relaxin\textsuperscript{43} in late gestation. These hormones are absolutely necessary for mammary development. Both sow-related processes (mammary development and colostrum production) are important at the time of farrowing.\textsuperscript{41} Thus, a “slight” asynchronism may lead to a major problem (PDS), similar to the butterfly effect.\textsuperscript{44} As hormonal changes start several days before farrowing, PDS also often starts a few days before farrowing.

Our understanding of the physiopathology of PDS implies three components (Figure 1): the body-building syndromes,\textsuperscript{35} the endotoxemia component linked to the innate immunity system, and stress-related mechanisms. Although they are closely related, we will now separate them for a didactical approach and highlight for each the new research findings available in the literature.

First, feed and feeding in gestation have straightforward consequences on body composition. One can note that, although there should be a natural peak of water intake just before parturition,\textsuperscript{46} this is rarely possible where a liquid feeding system is used (eg, as in France, Denmark, the Netherlands, and Spain). Surprisingly, while physiological and behavioral changes are well described in sows,\textsuperscript{35,41,47-50} a few exceptions remain, for example, drinking behavior around the time of parturition is not often discussed, although it may consequently interfere with homeorhesis.\textsuperscript{1}

When studying homeorhesis in gestation, it is necessary to take into account the fact that major changes have occurred in our sows since 2000. The two major changes are related to hyperprolificacy and carcass leanness. In 1998, Eggert et al\textsuperscript{57} had already observed that pig genotypes differed not only in the total amount of backfat, but also in the relative amounts of the three individual backfat layers. Backfat is a critical energy source for sows during periods of negative energy balance, and the relative contributions of each layer as a source of energy appear to differ. More broadly, fat has been shown important for endocrine regulation, including that of reproduction.\textsuperscript{51}

From a chronological point of view, we had the “thin sow syndrome” during the late 1970s, followed a few years later by the “fat sow syndrome,” and then what we called the “accordion sow syndrome,”\textsuperscript{52} describing sows that are too fat at farrowing, lose too
Initial recognition of microbes by cells of the immune system is largely based on pattern-recognition receptors, including Toll-like receptors (Toll-like receptor 4 is the main pattern-recognition receptor for lipopolysaccharides from gram-negative bacteria). No single organ is responsible for the origin of endotoxins, although the gut microflora is now recognized as probably the most important source. Indeed, in addition to its classical metabolic functions, the gut microflora has a major effect on innate immunity. A change in composition of the gut microbial community occurs at farrowing in sows, probably reflecting a peripartum digestive transit slow-down, which in turn is probably associated with concurrent hormonal changes. As sows approach farrowing, mild constipation is thus a common state. Even doubling the crude fiber content of the diet (from 3.8% to 7.0%) as the sow approaches farrowing reduces but does not prevent prolonged constipation. Besides the direct effect of fiber on digestive transit, an indirect effect has been described (but not explained) wherein sows fed high-fiber diets had a higher postpartum level of plasma prolactin than did control sows. This participates in making the “gut axis” so important in regard to the pathophysiology of PDS. In agreement with Reiner et al., we believe that a major pathophysiological component of PDS is triggered by bacterial endotoxins. As a consequence, these authors put emphasis on distinguishing fever and hyperthermia and the controversial cut-off between the two. Klopfenstein et al. for example, thoroughly discussed the value of 39.5°C that is often reported for diagnosis of fever and PDS. Rectal temperature is easy to measure, and it remains the parameter chosen to differentiate control sows from PDS sows. According to Reiner et al., the increase in rectal temperature is probably associated with the release of cytokines via macrophage activation. This would explain why an efficient treatment of PDS with non-steroidal anti-inflammatory drugs (NSAIDs) is often reported. Native immunity, which has been clearly related to the mammary gland in cattle, is less recognized by practitioners than is adaptive immunity. Recently, a team from Poland showed that sows that developed PDS had higher levels of two proinflammatory cytokines, tumor necrosis factor α (TNFα) and IL-6, 12 to 24 hours and 2 to 3 days before farrowing, respectively. These cytokines also increased after experimental infection with E. coli or administration of endotoxins, which may be explained by the fact that PDS is mainly produced by endotoxin-activated macrophages and is part of the activation processes of other cytokines, such as IL-6. Interestingly, recent results also support the hypothesis that polymorphisms of IL-6 and TNFα are associated with variations in amount of body fat within pig breeds. For example, the TNF gene is in a region where several quantitative trait loci for backfat thickness were also mapped.

Finally, stress is a classical pathway involved in PDS. Papadopoulos et al. reported that many risk factors for PDS are related to stress, such as late introduction of sows into farrowing crates. Bäckström et al. reported that incidence of MMA is greater in sows subjected to major changes in their environment, such as being moved from pasture to crates a few days before farrowing. However, allowing the sows to adapt to the new environment (farrowing crates) for 25 days before parturition, rather than 3 to 5 days, was not associated with a lower incidence of problem litters. It has been demonstrated that confinement at the time of strong nest-building motivation, immediately prior to parturition, resulted in physiological stress in the sow. Thus, a period of acclimatization to the new farrowing-lactation environment appears to be necessary to reduce stress.

Three recent studies showed a relationship between stress and farrowing duration and between control of stress and colostrum production. This indirect evidence attributes a major role in PDS to stress. An example of the linkage between the three components (body building, endotoxemia, and stress) of our proposed pathophysiology of PDS is the close relationship between the stress pathway and that of innate immunology. Thus, a current hypothesis of the effects of stress on immunity, which is based largely on data from rodents and humans, suggests that stress disrupts the balance between cellular immunity (T helper 1; Th1) and humoral immunity (T helper 2; Th2) in an attempt to achieve homeostasis (but not homeorhesis). This hypothesis holds that stress hormones influence the production of T helper cell (Th1 and Th2) cytokines, which determine the type of immune response that prevails. Cytokines provide the link between the innate and
Evolution from MMA to PDS

We propose to consider that MMA syndrome is the emerging part of an iceberg represented by PDS, with MMA now less common than it was 20 years ago. The following hypotheses may explain this shift. During the past 2 decades, radical changes in feeding management of sows have occurred in Western Europe. These are not fully implemented worldwide, while genetic lines have been harmonized across countries much faster. It is now unusual to feed a single sow diet throughout the reproductive cycle. The common practice is to feed different gestating and lactating sow diets, or to use a sophisticated multiple-phase diet – a practice that is increasingly observed. “Single” diets were formulated to provide 160 to 165 g per kg crude protein (CP) with ingestion of 480 to 495 g CP per sow per day (3 kg feed allowance per day). Current practice has reduced the protein by 33% during the gestation period (130 g CP per kg, 2.5 kg feed allowance per day). Concurrent with these changes in protein levels is a shift in energy sources: diets previously based on grains (high starch) now include a larger share of by-products rich in plant cell walls, with positive effects on MMA prevention as speculated by Gøransson and recently verified. Development of a specific net-energy system for sows allowed cost-effective, early implementation of such feeding strategies. These changes are depicted in Figure 3, showing the evolution of crude fiber (CF) and neutral detergent fiber (NDF) in gestating sow diets, based on trials reported at annual swine research meetings in France from 1985 to 2012 (Journées de la Recherche Porcine, nutrition sessions). The list of papers is available at www.aasv.org/. All trials related to sow feeding and showing the full ingredient composition of the gestation or lactation diets or both were selected to build the database. Nutrient contents were calculated from 75 recipes designed for gestating sows using the same database to ease comparison (EvaPig version 1.3.0.4; Ajinomoto-Eurolysine and INRA; 2012; available at http://www.evapig.com/x-home-en). A steady and progressive trend of increasing adaptive immune systems and help maintain T-cell homeostasis during infection. Stress can suppress, enhance, or have no effect on the immune status of an animal. Many of the conflicting findings reported may be partially explained by the animal (eg, genotype, age, social status), types of stressors, and management timing.

Conclusions

As reported by Pijoan et al in 2004, there is an evolution among diseases. Acute mastitis is much less common today. However, early postpartum disorders are more frequent, for example, neonatal diarrhea or low weaning weight (common consulting request to one author [GPM] by practitioners; unpublished data). These “new” problems occur in very good herds where productivity is very high and management skills are developed. Thus, numerous different but interacting mechanisms that are reflected by PDS affect the optimum expression of the sows’ productive capacity in a way that is much less clinically visible than was the MMA syndrome.

The central concept for an understanding of how a slight change related to the

Figure 3: Steady rise of crude fiber (CF) and neutral detergent fiber (NDF) content in gestating sow diets reported at the nutrition sessions of the Journées de la Recherche Porcine (France) from 1985 to 2012. The list of papers is available at www.aasv.org/.

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animals or to their management can lead to major (although not spectacular) problems is homeorhesis and its critical shift occurring around the time of farrowing. Therefore, at parturition, "the orchestrated or coordinated changes in metabolism of body tissues necessary to support a (dominant) physiological state" have to shift from a priority of gestation to a priority of lactation. Many of these modifications occur before farrowing, but remain asymptomatic until revealing animals such as piglets are present. The shift from homeorhesis of gestation to homeorhesis of lactation has not yet been taken into account in proposals for the pathophysiology of PDS, probably because physiology, endocrinology, and clinical innate and adaptive immunology all must be simultaneously considered.

Conflict of interest
None reported.

References


*Non-refereed references.*