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Estrategias para mejorar la calidad del calostro en el ganado caprino y la inmunidad adquirida en cabritos

Strategies to improve colostrum quality in dairy goats and the acquired immunity in goat kids

MARTA GONZÁLEZ CABRERA

ESCUELA DE DOCTORADO

DOCTORADO EN SANIDAD ANIMAL Y SEGURIDAD ALIMENTARIA

LAS PALMAS DE GRAN CANARIA

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TESIS DOCTORAL

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UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA
Escuela de Doctorado

D. ANTONIO J. FERNÁNDEZ RODRÍGUEZ, COORDINADOR DEL PROGRAMA DE DOCTORADO DE SANIDAD ANIMAL Y SEGURIDAD ALIMENTARIA DE LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA

INFORMA,

De que la Comisión Académica del Programa de Doctorado, en su sesión de fecha ...../...../....., tomó el acuerdo de dar el consentimiento para su tramitación, a la tesis doctoral titulada "**Estrategias para mejorar la calidad del calostro en el ganado caprino y la inmunidad adquirida en cabritos**" presentada por la doctoranda Dª **Marta González Cabrera** y dirigida por el Dr. D. **Lorenzo Enrique Hernández Castellano** y la Dra. Dña. **Noemí Castro Navarro**.

Y para que así conste, y a efectos de lo previsto en el Artº 11 del Reglamento de Estudios de Doctorado (BOULPGC 04/03/2019) de la Universidad de Las Palmas de Gran Canaria, firmo la presente en Arucas, a .... de ..... de dos mil veinticinco.

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UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA

ESCUELA DE DOCTORADO

Programa de doctorado

DOCTORADO EN SANIDAD ANIMAL Y SEGURIDAD ALIMENTARIA

Título de la Tesis Doctoral

Estrategias para mejorar la calidad del calostro en el ganado caprino y la inmunidad adquirida en cabritos

Strategies to improve colostrum quality in dairy goats and the acquired immunity in goat kids

Tesis Doctoral presentada por

MARTA GONZÁLEZ CABRERA

Dirigida por

Dr. LORENZO ENRIQUE HERNÁNDEZ CASTELLANO

Dra. NOEMÍ CASTRO NAVARRO

Arucas, a ..... de .....de 2025

EL DIRECTOR **LA DIRECTORA** **LA DOCTORANDA**

A mis padres

“Animal research is a privilege only a few are lucky enough to experience”

PREFACIO

La presente Tesis Doctoral se integra en un proyecto de investigación competitivo subvencionado por la Agencia Canaria de Investigación, Innovación y Sociedad de la Información (ACIISI) del Gobierno de Canarias (PROID2021010035). Este proyecto tiene por objetivo el estudio y desarrollo de nuevas estrategias que permitan la manipulación de la barrera sangre-leche mediante la administración vía intramamaria de lipopolisacáridos bacterianos para así mejorar la producción y calidad del calostro y leche en cabras de raza Majorera y la inmunidad adquirida en cabritos. Asimismo, se desarrollaron otros ensayos de forma paralela al proyecto de investigación cuyos resultados también se integran en la presente Tesis Doctoral. Todos los protocolos experimentales recibieron la aprobación por parte del Comité de Ética para la Experimentación Animal de la Universidad de Las Palmas de Gran Canaria (procedimientos OEBA-ULPGC 27/2021, OEBA-ULPGC 28/2021, OEBA-ULPGC 03/2023 y OEBA-ULPGC 04/2023).

El proyecto de investigación estaba concedido en el momento en el que comenzaron los estudios de doctorado, por lo que el diseño experimental ya estaba establecido. Sin embargo, la ejecución de todos los ensayos, la recogida, procesado y los análisis de las muestras fueron realizados por mí bajo la dirección del Dr. Lorenzo Enrique Hernández Castellano y la Dra. Noemí Castro Navarro. Asimismo, el análisis estadístico de los datos, interpretación de los resultados, la redacción de los manuscritos y su presentación fueron realizados por mí con la colaboración del resto de autores.

La literatura previa sobre las diversas áreas de interés encuadradas en la presente Tesis Doctoral se recoge en el Capítulo 2 con el objeto de presentar los antecedentes y exponer las necesidades de la investigación que derivan en los objetivos planteados. El Capítulo 3 tiene como objetivo describir los complejos mecanismos fisiológicos que intervienen en la síntesis de calostro y evidenciar el impacto de las estrategias nutricionales, el manejo del secado y la estimulación de la respuesta inmune local sobre la calostrogénesis. En el Capítulo 4 se presentan los resultados derivados de un ensayo experimental en el que se evaluó el efecto del incremento de almidón en la dieta durante el último mes de gestación sobre la producción y composición del calostro y leche en cabras Majoreras, así como sobre el crecimiento, estado inmune y metabólico de los

cabritos. Los Capítulos 5 y 6 recogen los resultados derivados del proyecto PROID2021010035 en el que se evaluó el efecto de la aplicación intramamaria de lipopolisacáridos bacterianos sobre la composición del calostro, el estado inmune de las cabras, y la inmunidad adquirida en los cabritos. Por último, en el Capítulo 7 se recogen los resultados derivados del estudio de las expresiones faciales de los cabritos como método para la detección de signos de dolor en estos animales.

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Capítulo 1

Introducción general

La mortalidad neonatal en el ganado caprino está directamente relacionada con la ingesta insuficiente y/o con una inadecuada calidad del calostro. Este es un factor clave en la cría de pequeños rumiantes y una de las principales causas de baja productividad en las explotaciones ganaderas de tipo lechero. Los rumiantes neonatos son vulnerables frente a procesos de origen infeccioso debido a la estructura placentaria de los rumiantes (Robertson et al., 2020). Por ello es fundamental garantizar un aporte de calostro de calidad, en el momento adecuado y en cantidades suficientes. Es frecuente que las cabras lecheras produzcan calostros de poca calidad y esto conlleva un fallo en la transferencia de inmunidad pasiva, lo que supone una merma en la salud de los animales neonatos y, por tanto, grandes pérdidas económicas para el sector.

Tal y como ha sido descrito en numerosos estudios, un mal manejo del período seco y la nutrición durante los últimos meses de gestación implica una reducción de la producción y calidad del calostro en ganado bovino (Gulliksen et al., 2008; Nowak et al., 2012), ovino (Banchero et al., 2004a, 2004b; Zarrin et al., 2021) y caprino (Caja et al., 2006; Castro et al., 2011b). Sin embargo, aún existe un gran desconocimiento sobre el efecto que tiene el manejo de las cabras lecheras durante el período seco y el parto en el proceso de formación tanto del calostro (calostrogénesis), como de los componentes bioactivos presentes en éste. Esta Tesis Doctoral pretende resolver las siguientes cuestiones: 1) si el aumento del contenido de almidón en la dieta durante el último mes de gestación incrementa la cantidad y calidad del calostro en cabras lecheras; 2) si el aumento del contenido de almidón en la dieta durante el último mes de gestación mejora el crecimiento, el metabolismo y la inmunidad adquirida en los cabritos durante el primer mes de vida; 3) si la administración intramamaria de lipopolisacáridos bacterianos en el momento del parto permite modular la permeabilidad de la barrera sangre-leche mejorando la composición del calostro 4) si la administración intramamaria de lipopolisacáridos bacterianos en el momento del parto mejora el rendimiento y la inmunidad adquirida en los cabritos durante el primer mes de vida 5) si la expresión facial de los cabritos puede ser usada para evaluar el dolor o malestar en éstos.

Capítulo 2

Revisión bibliográfica

2.1. LA MORTALIDAD NEONATAL EN EL GANADO CAPRINO Y LA IMPORTANCIA DEL CALOSTRO

En los últimos años, la industria caprina ha mostrado un crecimiento exponencial debido, entre otros, a los cambios en las preferencias de los consumidores, así como la tecnificación tanto de la cría como del manejo de estos animales. Según la Organización de las Naciones Unidas para la Alimentación y la Agricultura (FAO,2022), existen más de mil millones de cabras en todo el mundo. El ganado caprino siempre ha tenido una gran relevancia social y cultural para muchas comunidades. De hecho, el Instituto Internacional de Investigación Ganadera ha reconocido que las cabras son más importantes en áreas menos favorecidas que el ganado bovino (Miller y Lu, 2019). Sus características biológicas han potenciado su supervivencia en condiciones ambientales adversas permitiéndoles ser la especie de rumiante con una de las distribuciones más amplias a nivel global (Simões y Gutiérrez, 2018).

Además de la escasez de alimentos y pastos en algunas áreas del planeta (Lérias et al., 2013), la ganadería caprina se enfrenta a importantes desafíos como el aumento de los precios de los piensos y la presencia de enfermedades infecciosas. Todo ello tiene un efecto negativo en la producción y una gran repercusión en la salud y el bienestar de los animales. De hecho, la preocupación creciente del consumidor por el bienestar de los animales de producción ha fomentado su estudio (Winckler et al., 2003; Anzuino et al., 2010; Phytian et al., 2011; Battini et al., 2014), promoviéndose el desarrollo de técnicas novedosas para la evaluación y detección precoz del dolor, así como otros problemas de salud en el ganado (Häger et al., 2017; Viscardi et al., 2017; Müller et al., 2019). Aunque se han identificado múltiples indicadores de bienestar en el ganado caprino, tales como la condición corporal, el estado del pelo o la postura, el desarrollo de métodos no invasivos aplicables en la práctica ganadera aún requiere de más estudios en esta especie (Battini et al., 2014). Asimismo, los productores de caprino lechero ponen de manifiesto otro problema económico y de bienestar, de gran importancia, la mortalidad neonatal (Rätsep, 2020). La muerte de cabritos en la primera semana de vida suele estar asociada con la presencia de neumonía, diarrea o inanición, entre otros problemas de salud. Aunque el momento de mayor mortalidad de los cabritos aún no está bien

definido, Bajhau y Kennedy (1990) observaron que la mayoría de las pérdidas ocurren dentro de los primeros días de vida y cuando el peso al nacimiento es inferior a 2,5 kg. Asimismo, Argüello et al. (2004a) observaron que los cabritos con un peso al nacimiento inferior a 2,5 kg tenían menores concentraciones de inmunoglobulinas en la sangre, lo que sugiere una mayor susceptibilidad a infecciones y, en consecuencia, un mayor riesgo de mortalidad. Varios estudios han abordado la mortalidad de cabritos antes del destete evidenciando que esta puede oscilar entre el 4,3% y el 57,7% (Tabla 1) y que depende de múltiples factores como el sistema de manejo, la salud de la madre, el peso corporal del cabrito al nacer, el tamaño de la camada, la estación y el grado de inmunización después de la ingesta de calostro (Perez-Razo et al., 1998; Chowdhury et al., 2002; Robertson et al., 2020). Los estudios sobre la mortalidad neonatal en caprino lechero en Europa son escasos, lo que dificulta la evaluación y caracterización de la problemática. Sin embargo, se sabe que la mortalidad neonatal está fuertemente relacionada con prácticas de manejo inadecuadas en los últimos dos meses de gestación (Caja et al., 2006; Castro et al., 2011b; Weaver et al., 2021). Durante este período, la glándula mamaria cesa la producción de leche y comienza una involución que finalmente culmina con la síntesis de calostro, también conocida como calostrogénesis. Este período es esencial no solo para garantizar un desarrollo óptimo de la gestación y lactación, sino también para la salud y el rendimiento de la descendencia.

Tabla 1. Mortalidad en cabritos antes del destete

Región/País	Tasa de mortalidad (%)	Raza	Sistema de manejo	Referencia bibliográfica
África				
Etiopía	31 – 42	Arsi-Bale/ Borana	Extensivo	Hailu et al. (2006)
Ghana	10	West African Dwarf	Intensivo	Turkson et al. (2004)
Marruecos	16	Beni Arouss/Northen Morocco	Extensivo	Bahri et al. (2021)
Sudáfrica	8,6 – 16,5	Angora	Extensivo	Snyman (2010)
América				
Canadá	20 -30	Saanen /Alpina	Intensivo	Rätsep (2020)
Estados Unidos	10 -14	n.e.	n.e.	USDA (2012)

Asia				
India	8,92 – 57,7	Sirohi /Local	Semi-intensivo	Chauhan et al., (2019); Perumal et al., (2019)
Jordania	13	Crossbred Shami	Extensivo	Aldomy et al., (2009)
Sri Lanka	23,74 – 32,19	South Indian/Local	Extensivo	Ranatunga (1971)
Europa				
Alemania	16,1 – 24,1	Alpina / Saanen	n.e.	Balasopoulou et al. (2022)
Holanda	4,3	n.e.	Intensivo	Dijkstra et al. (2023)
España	21	MG / MG x Boer	Intensivo	Fernández et al. (2021)
Oceanía				
Australia	20	Boer / Kalahari Red	n.e.	Robertson et al. (2020)
Nueva Zelanda	5,9 – 20,5	n.e.	Intensivo	Todd et al. (2019)

Fuente: Revisión (Capítulo 3); **Abreviaciones:** n.e. = no especificado; MG = Murciano-Granadina.

A diferencia de otros mamíferos, los rumiantes no transfieren suficientes componentes inmunes durante la gestación debido a que su placenta es epiteliocorial (Green et al., 2021; Bigler et al., 2022). Como resultado, los rumiantes recién nacidos dependen estrictamente de la ingesta de calostro, no solo como fuente de nutrición, sino también para adquirir componentes inmunes de origen materno. Además, el calostro debe ingerirse en las primeras horas de vida (Castro-Alonso et al., 2008; Moretti et al., 2012, 2013) ya que la permeabilidad intestinal disminuye rápidamente, reduciendo la capacidad del organismo para absorber determinadas macromoléculas como, por ejemplo, las inmunoglobulinas. El calostro contiene nutrientes esenciales como lactosa y triglicéridos que pueden ser metabolizados para producir energía e inducir la termogénesis. De hecho, la temperatura rectal en terneros recién nacidos aumenta dentro de las primeras horas después del consumo de calostro, contribuyendo a la supervivencia de estos animales en condiciones ambientales adversas (Kirovski, 2015). El calostro también proporciona diversas moléculas bioactivas tales como, inmunoglobulinas, factores de crecimiento, péptidos, enzimas y hormonas que pueden ser absorbidas y desempeñar una acción sistémica y/o local durante los primeros días de vida. Además de su papel en la inmunidad adquirida, el calostro también promueve

el desarrollo y la salud del tracto gastrointestinal de los recién nacidos. Según Kargar et al. (2020) y McCarthy et al. (2024), una alimentación prolongada con calostro durante las primeras dos semanas de vida puede aumentar la ganancia de peso diaria y reducir la susceptibilidad a sufrir diarrea y neumonía en terneros. Todos estos componentes son vitales para asegurar la supervivencia del recién nacido, siendo la concentración de estos dependiente de múltiples factores como la especie, la raza, la nutrición y salud de la madre (Hernández-Castellano et al., 2016; Soufleri et al., 2021).

2.1.1. CALIDAD DEL CALOSTRO

Debido al importante papel que tiene el calostro en la supervivencia y desarrollo de los rumiantes neonatos, la determinación de su calidad ha adquirido gran relevancia tanto para los productores, como para el sector comercial y científico. La calidad del calostro suele determinarse principalmente por su concentración de inmunoglobulina G (IgG), que actualmente se considera el principal indicador de la transferencia de inmunidad pasiva (TPI). La concentración de IgG en el calostro puede medirse mediante radioinmunoensayo, electroforesis, ensayo de inmunoadsorción ligado a enzimas (ELISA) y mediante inmunodifusión radial (Weaver et al., 2000). Además, también existen métodos de estimación práctica en la granja como los calostrómetros (Bartier et al., 2015), refractómetros ópticos o digitales (Castro et al., 2018; Pérez-Marín et al., 2023) y evaluaciones visuales de color (Argüello et al., 2005). Estas técnicas proporcionan herramientas accesibles en la granja permitiendo a investigadores, veterinarios y ganaderos evaluar eficazmente la calidad del calostro.

A pesar de que la mayoría de los estudios sobre el calostro en rumiantes se han desarrollado en vacas lecheras, no existe una definición clara de la calidad, ni ésta puede extrapolarse a otras especies, ya que se sabe que difiere significativamente entre especies y razas (Wheeler et al., 2007; Stelwagen et al., 2009; Kessler et al., 2019). Actualmente, los valores de referencia para definir un calostro de buena calidad se han establecido en ≥ 50 mg/ml de IgG para el ganado bovino (Weaver et al., 2000) y ≥ 20 mg/ml de IgG para el ganado caprino (Tabla 2; Argüello et al., 2005; Castro et al., 2005; Kessler et al., 2021). Asimismo, las concentraciones de IgG y proteína total sérica ≥ 10mg/ml y ≥ 6,2 g/dl, en terneros, y ≥ 11,4 mg/ml y ≥ 4,6 g/dl (Tabla 2) en corderos y cabritos, respectivamente han sido aceptadas como valores de referencia para

determinar una correcta transferencia de inmunidad pasiva (Weaver et al., 2000; Lombard et al., 2020; Zamuner et al., 2023). Definir estos parámetros de calidad ha sido esencial para mejorar las prácticas de manejo del encalostrado en pequeños rumiantes, las cuales han sido previamente revisadas por Castro et al. (2011b). Para facilitar las prácticas de manejo en las granjas se han implementado herramientas de fácil y rápida utilización como la refractometría de grados Brix, puesto que existe una alta correlación entre las concentraciones de IgG en calostro y suero sanguíneo con los grados Brix (Kessler et al., 2021). Según la literatura, los valores Brix del calostro ≥ 22° en ganado bovino (Chigerwe y Hagey, 2014), ≥ 26° en ovino (Hamer et al., 2023) y ≥ 20° en caprino (Tabla 2; Kessler et al., 2021) son indicativos de un calostro de buena calidad.

Por todo lo anterior, resulta fundamental la ingesta de calostro de calidad en el momento adecuado para garantizar la adquisición de una correcta transferencia de inmunidad pasiva reduciendo así el riesgo de morbilidad y mortalidad neonatal en rumiantes.

Tabla 2. Valores de referencia para la transferencia de inmunidad pasiva en el ganado caprino

Calostro		Suero sanguíneo	
IgG (mg/ml)	Brix (°)	IgG (mg/ml)	Brix (°)
≥ 20	≥ 20	≥ 11,4	≥ 8,6 – 9,3

Fuente: Batmaz et al. (2019); Brioso et al. (2023); Zamuner et al. (2023)

2.2. FISIOLOGÍA DURANTE EL FINAL DE LA GESTACIÓN

El período que incluye los dos últimos meses de gestación también se conoce como período seco. Los cambios fisiológicos que acontecen durante esta etapa son fundamentalmente adaptativos y preparan a la hembra para la expulsión del feto y la transición entre el final de la gestación y el comienzo de la lactación. La fisiología del bovino ha sido tomada como modelo por ser la especie con mayor relevancia y aportación a la industria lechera a nivel mundial, sin embargo, el estudio del ganado ovino y caprino ha adquirido mayor relevancia en las últimas décadas (Lérias et al., 2014; Hernández-Castellano et al., 2016; Zamuner et al., 2020).

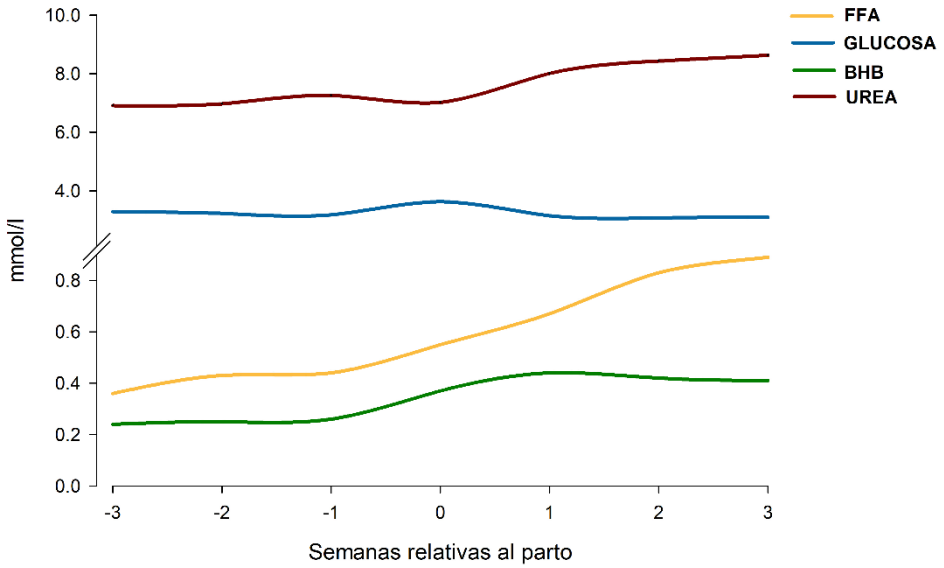
2.2.1. CAMBIOS METABÓLICOS Y HORMONALES

Tal y como afirmaba Lavoisier, la vida es un proceso químico que implica la combinación de múltiples mecanismos moleculares (Lavoisier, 1789). La gestación y la lactación son considerados estados de homeorresis, que se definen como aquellos cambios metabólicos coordinados hormonalmente que tienen lugar para atender las demandas fisiológicas del organismo con el fin último de alcanzar el equilibrio fisiológico, también conocido como homeostasis (Bauman y Currie, 1980). Durante las últimas fases de la gestación, se pueden observar múltiples cambios metabólicos y hormonales relacionados con el crecimiento de los fetos y el desarrollo de la glándula mamaria en preparación para el comienzo de la lactación. Según Bauman y Currie (1980) el 70% del crecimiento fetal tiene lugar durante las últimas seis semanas de gestación. Durante este período, la cavidad abdominal se expande y se produce una compresión del tracto gastrointestinal que resulta en una reducción de la capacidad de ingesta la cual se intensifica en gestaciones con más de un feto (Sauvant et al., 2018).

Si bien los cambios metabólicos durante el período de transición en el ganado bovino lechero han sido objeto de numerosos estudios (Bauman y Currie, 1980; De Koster y Opsomer, 2013; Haisan et al., 2021; Rossi et al., 2023), la investigación de este período en el ganado caprino lechero sigue siendo muy limitada. La alta demanda energética en los animales con elevada prolificidad y capacidad productiva resulta en un incremento del balance energético negativo (NEB). Todo ello implica una serie de adaptaciones metabólicas (Zamuner et al., 2020) tales como la intensificación de la gluconeogénesis y la lipólisis; procesos que desencadenan un aumento de la movilización y catabolismo de las reservas lipídicas. La metabolización de los lípidos resulta en una elevación de metabolitos como el β-hidroxibutirato (BHB) y los ácidos grasos libres (FFA) en sangre (Figura 1; Banchero et al., 2004a, 2004b; Zamuner et al., 2020). Estos metabolitos resultantes del catabolismo graso son biomarcadores de un NEB. A pesar de todo, las cabras son menos propensas a desarrollar toxemia de gestación y/o cetosis de lactación en comparación con las ovejas y las vacas lecheras, respectivamente (Pezzanite et al., 2009; Marutsova y Binev, 2017), por lo que la concentración de cuerpos cetónicos (BHB) en esta especie no suele superar los 0,8 mmol/l durante el período de transición (Marutsova y Binev, 2017; Zamuner et al., 2020). A medida que avanza la gestación se

produce una disminución gradual de la concentración de glucosa y un incremento abrupto en el momento del parto (Figura 1; de Souza Castagnino et al., 2015; Zamuner et al., 2020). Como resultado de ese NEB, también se observa el aumento significativo de las concentraciones de urea relacionadas con una intensificación del catabolismo de aminoácidos (Figura 1; Radin et al., 2015; Soares et al., 2018), una disminución del consumo diario de materia seca o incluso cambios en la eficacia de utilización del nitrógeno (Brun-Bellut, 1997). También se puede observar un incremento de la concentración de lactato deshidrogenasa (LDH), asociado con un incremento de la producción de lactato en el rumen debido al aporte de dietas basadas en un alto contenido en concentrado (De Koster y Opsomer, 2013). No obstante, siempre se debe tener en cuenta que los perfiles metabólicos pueden variar dependiendo de la especie, el genotipo, el rendimiento lechero, la composición de la dieta y el sistema productivo entre otros factores (de Souza Castagnino et al., 2015; Overton et al., 2017).

Figura 1. Cambios metabólicos durante el período de transición en cabras lecheras



Fuente: Zamuner et al. (2020); **Abreviaciones**: FFA = ácidos grasos libres; BHB = β-hidroxibutirato.

Además del crecimiento de los fetos, durante las últimas semanas del período seco se produce la acumulación de nutrientes y componentes bioactivos en la glándula mamaria. Este proceso involucra mecanismos moleculares complejos, en los cuales el sistema neuroendocrino juega un papel importante (Bigler et al., 2023). Durante las

últimas semanas de gestación, la concentración de progesterona en sangre disminuye progresivamente hasta 24 horas previas al parto donde se observa una caída brusca, mientras que durante este mismo período se observa un aumento constante de los estrógenos alcanzando su concentración máxima en el momento del parto (Henricks et al., 1972). Al mismo tiempo, se observa un aumento de la hormona del crecimiento, la cual favorece la distribución de nutrientes hacia la glándula mamaria estimulando el flujo sanguíneo, la gluconeogénesis y la lipólisis (Zamuner et al., 2020). Asimismo, la insulina posee un papel importante al final de la gestación ya que es responsable de controlar el metabolismo de la glucosa (De Koster y Opsomer, 2013). Esta hormona limita la utilización de glucosa en los tejidos periféricos maternos con el fin de aumentar su disponibilidad para el crecimiento fetal y el desarrollo de la glándula mamaria (Bell y Bauman, 1997; De Koster y Opsomer, 2013). El incremento de otras hormonas como la oxitocina, la prostaglandina F2α y el cortisol desempeñan su función al final de la gestación, desencadenando el comienzo del parto y asegurando una correcta progresión y expulsión de los fetos (Kindahl et al., 2002).

2.2.2. REQUERIMIENTOS NUTRICIONALES

La gestación y lactación se solapan durante, aproximadamente, tres meses en el ciclo productivo del ganado caprino, por lo que el comienzo de la gestación en pequeños rumiantes tiene lugar en torno a los 90-150 días de lactación. De forma similar al bovino lechero, los meses de secado coinciden con los dos últimos meses de gestación, período durante el cual tiene lugar un incremento de los requerimientos nutricionales debido a múltiples cambios fisiológicos asociados al término de la gestación (desarrollo fetal y síntesis de calostro). La mayor parte del desarrollo de la glándula mamaria ocurre durante el último mes de gestación (Davis y Collier, 1985). De hecho, en la semana previa al parto la glándula mamaria aumenta notablemente de tamaño (Mellor, 1987; Mellor et al., 1987) y comienza la síntesis masiva de calostro (Hartmann, 1973). Tanto el crecimiento de la glándula como la diferenciación de las células mamarias están fuertemente influenciados por la nutrición de la madre durante la última etapa de la gestación (Banchero et al., 2015). Una buena parte de los sistemas de producción de ganado caprino en Europa siguen las pautas de alimentación del sistema francés (*L´Institut Nationale de la Recherche Agronomique*; INRA) actualizadas por última vez en

el año 2018 (Sauvant et al., 2018). Sin embargo, también existen otras guías nutricionales usadas a nivel internacional como la americana (*National Research Council;* NRC) o la australiana (*Commonwealth Scientific and Industrial Research Organisation*; CSIRO). Los modelos propuestos en estos trabajos utilizan las razas caprinas Saanen y Alpina para estimar los requerimientos de energía y proteína metabolizables. De acuerdo con Sauvant et al. (2018) las necesidades energéticas crecen exponencialmente durante la gestación y vienen determinadas por el tamaño de la camada y el peso de los fetos. En el contexto de la producción intensiva, las necesidades energéticas, de proteínas y minerales están asimismo condicionadas por la capacidad de ingesta, la cual se reduce a medida que progresa la gestación (Tabla 3).

Tabla 3. Necesidades nutricionales en cabras* durante la gestación

Mes	Producción (Kg)	MS (kg)	PDI (g)	UFL/j	UEL/j	Ca_{abs} (g)	P_{abs} (g)
1	1,5	1,5	127	1,45	1,66	4,7	3,6
2	1,2	1,5	114	1,35	1,60	4,4	3,4
3	1	1,4	100	1,26	1,54	4,2	3,2
4	-	1,14	56	1,12	1,2	3,8	2,9
5	-	1,14	99,5	1,73	1,2	5,4	4,2

Fuente: Adaptado de Sauvant et al. (2018); ***** = cabra adulta de 60 Kg en gestación con dos fetos.
Abreviaciones: MS = Materia seca; PDI = proteína digestible en el intestino; UFL = energía neta para lactación; UEL = capacidad de ingesta; Ca_{abs} = calcio absorbible; P_{abs} = fósforo absorbible.

Si bien es cierto que estas recomendaciones están ampliamente aceptadas, existen numerosas razas de caprino con necesidades muy diversas. Es por ello, que en las últimas décadas, la nutrigenómica se convertido en un área de gran interés (Chadwick, 2004; Lu, 2024). Los avances en las prácticas de manejo nutricional en pequeños rumiantes han conducido a un mejor conocimiento sobre la interacción molecular entre los nutrientes y otros componentes bioactivos de la dieta con la expresión génica, contribuyendo de esta manera a una mejor comprensión de la utilización y los requerimientos nutricionales durante la gestación y la lactación (Osorio et al., 2017; Kyriakaki et al., 2023). De hecho, algunos autores han evidenciado los efectos de la suplementación energética, con hidratos de carbono, proteínas y de grasa al final de la gestación sobre el metabolismo y la calidad del calostro en ganado bovino, ovino y

caprino (Bell et al., 2000; Banchero et al., 2006; Celi et al., 2008). Estos hallazgos destacan la importancia de una nutrición adecuada y estratégica en las últimas fases de la gestación para la producción de un calostro de buena calidad.

2.2.3. DESARROLLO DE LA GLÁNDULA MAMARIA

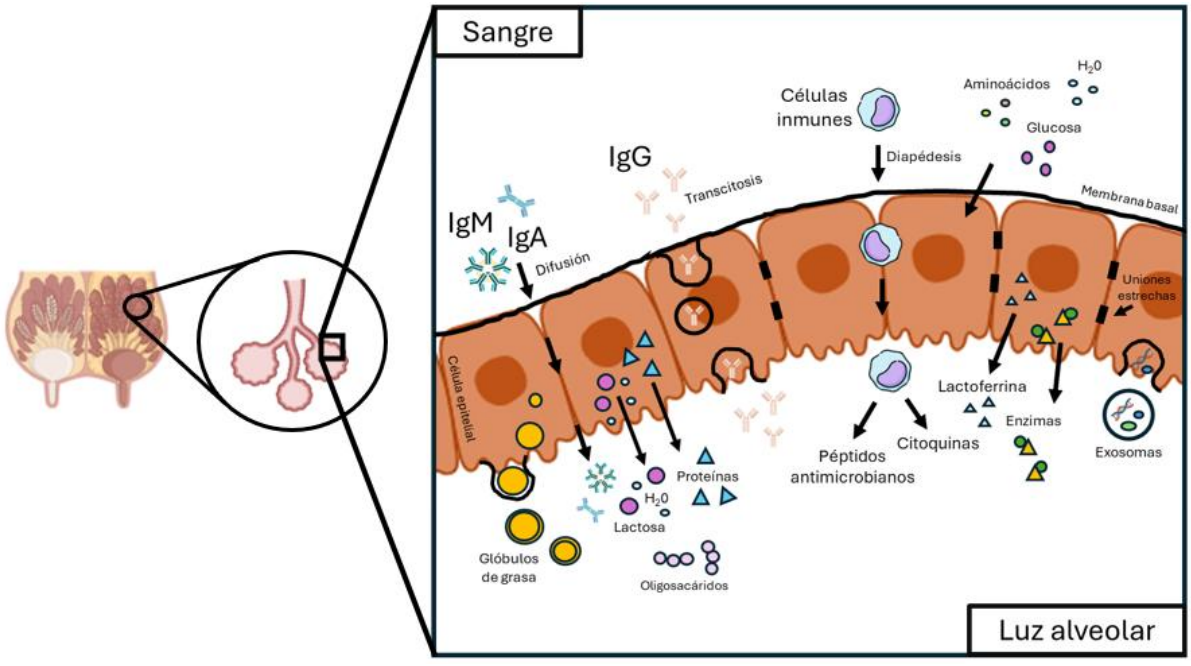
La formación y el desarrollo de la glándula mamaria tiene lugar en dos etapas, embrionaria y postnatal. Los primeros cambios funcionales comienzan antes del nacimiento en una fase denominada mamogénesis, la cual perdura hasta el comienzo de la primera lactación (Knight y Peaker, 1982). Posteriormente durante la pubertad y vida adulta se producen una serie de cambios morfológicos y funcionales que se dividen en cuatro etapas cíclicas, 1) la calostrogénesis o lactogénesis I, etapa en la que tiene lugar la síntesis y secreción del calostro; 2) la lactogénesis II, etapa que corresponde con el comienzo de la producción de leche; 3) la galactopoyesis o mantenimiento de la lactación y, 4) la involución o regresión del parénquima mamario. En el contexto de la producción intensiva, es frecuente el solapamiento entre el final de la lactación y una nueva gestación con el fin de optimizar la producción (Knight y Peaker, 1982). De modo que a medida que progresa la gestación, la producción láctea cesará para permitir la involución de la glándula mamaria, la cual precederá al comienzo de un nuevo ciclo productivo.

El comienzo de una nueva lactación se acompaña de múltiples cambios celulares, tales como la proliferación, la apoptosis, la diferenciación celular y cambios en la expresión génica (Knight y Peaker, 1982; Hou et al., 2017). Durante la mamogénesis en animales primíparos, la glándula mamaria se compone de un sistema de conductos muy poco desarrollado y rodeados por un extenso depósito graso. Durante la gestación se observa un aumento del tamaño y complejidad del sistema de conductos y una proliferación de las células epiteliales, desplazando el tejido adiposo y formando el primer tejido alveolar funcional (Knight y Peaker, 1982).

A nivel histológico, los alveolos están formados por acinos glandulares y éstos, a su vez, están constituidos por células endoteliales y mioepiteliales, tejido conectivo y una membrana basal donde se alojan las células epiteliales responsables de la síntesis de calostro y leche (Cowie et al., 1952; Howe et al., 1975). A esta estructura se le conoce

como barrera sangre-leche (BMB; Bruckmaier y Wellnitz, 2017) y es la encargada de regular el intercambio de sustancias entre la sangre y la luz alveolar (Wheeler et al., 2007). Las células epiteliales están estrechamente conectadas entre sí mediante complejos de unión conocidos como desmosomas, hemidesmosomas y uniones estrechas (Nguyen y Neville, 1998). Son estas últimas las que cobran mayor importancia a la hora de separar los vasos sanguíneos, el líquido extracelular y los compartimentos que contienen calostro o leche, evitando un intercambio indiscriminado de componentes solubles y celulares (Wellnitz et al., 2016). Se ha demostrado que las uniones estrechas son más laxas y, por tanto, más permeables durante gestación, probablemente con el fin de favorecer el transporte de nutrientes, moléculas y células inmunes durante la calostrogénesis (Nguyen y Neville, 1998; Wall et al., 2015). No obstante, las uniones estrechas del epitelio mamario son dinámicas y pueden ser reguladas por diversos estímulos como la acumulación de leche en la ubre, altas dosis de oxitocina o la mastitis (Lehmann et al., 2013; Wall et al., 2016; Wellnitz et al., 2016).

Figura 2. Estructura de la barrera sangre-leche y mecanismos de secreción

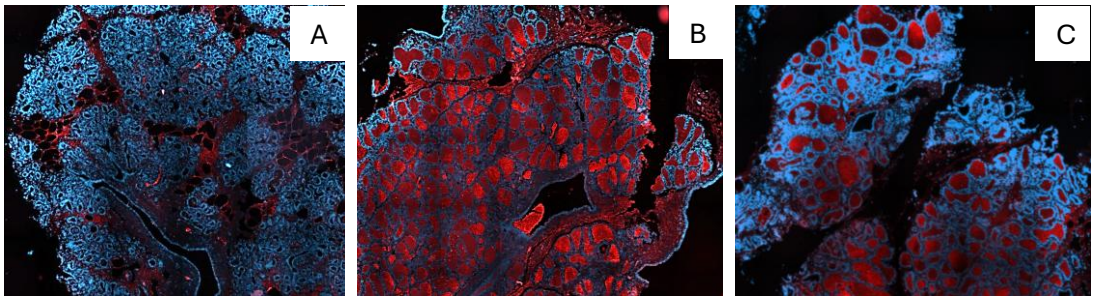


Fuente: Wheeler et al. (2007); Hernández-Castellano et al. (2014); Baumrucker et al. (2021);
Abreviaciones: IgG = Inmunoglobulina G**;** IgM = Inmunoglobulina M; IgA = Inmunoglobulina A.

2.2.4. SÍNTESIS DEL CALOSTRO

La insuficiente transferencia de componentes inmunes durante la gestación unida a un sistema inmunitario inmaduro durante las primeras semanas de vida representa una gran desventaja para los rumiantes recién nacidos (Argüello et al., 2004c; Castro et al., 2009). La función de esta glándula sudorípara modificada es la de crear una secreción nutritiva y protectora con el objetivo de garantizar una descendencia viable (Playford y Weiser, 2021). La mayoría de los componentes presentes en el calostro y sus precursores alcanzan la secreción mamaria a través de las células epiteliales, mediante mecanismos de transporte celular activo, endocitosis y exocitosis, o mediante una difusión pasiva o paracelular (Wheeler et al., 2007; Wall et al., 2015). Nutrientes como la lactosa, la proteína y la grasa son absorbidos y/o sintetizados por las células epiteliales, al igual que ocurre con otros componentes como los oligosacáridos, la lactoferrina, los péptidos, las enzimas y las hormonas (Wheeler et al., 2007). Sin embargo, la mayor parte de las inmunoglobulinas (IgG_1; Figura 3) se transfieren al calostro selectivamente mediante receptores específicos como el receptor Fc neonatal (FcRn) cuyo papel durante la calostrogénesis ha sido descrito en profundidad por Baumrucker et al. (2021). Otras moléculas, como la IgG_2 o la albúmina sérica, alcanzan la luz alveolar mediante difusión pasiva cuando la permeabilidad de la BMB aumenta, ya que en circunstancias normales son recicladas al espacio intercelular (Wall et al., 2015; Wellnitz et al., 2015; Baumrucker et al., 2023). Sin embargo, algunos autores han puesto de manifiesto la posibilidad de una síntesis local de inmunoglobulinas durante la calostrogénesis, ya que las concentraciones de IgG circulantes no justifican la masa total de IgG acumuladas en el calostro (Lascelles, 1979; Baumrucker et al., 2021). Aunque aún se desconocen los mecanismos que lo regulan, algunos estudios sugieren que el origen de estas inmunoglobulinas puede estar en las células inmunes presentes en el tejido mamario (Aitken et al., 2011; Baumrucker et al., 2021).

Figura 3. Inmunofluorescencia para IgG total (rojo) en biopsias de tejido mamario de vaca Holstein los días -21 (A), -7 (B) relativos al parto y el día del parto (C)



Fuente: Imágenes cedidas por Dr. Michael Steele (University of Guelph).

2.2.4.1. CONTROL HORMONAL DE LA CALOSTROGÉNESIS

Aunque los mecanismos endocrinos que regulan la calostrogénesis no están completamente definidos, no existe una hormona específica que controle este proceso en los rumiantes. En su lugar, la calostrogénesis parece estar regulada por varias hormonas que actúan de forma coordinada en diferentes etapas de la síntesis del calostro. En las últimas dos o tres semanas antes del parto se produce una reducción progresiva de la progesterona (Henricks et al., 1972; Barrington et al., 2001) y de forma simultánea, el aumento de ciertas hormonas galactopoyéticas como la prolactina y el lactógeno placentario, así como los estrógenos, que promueven la transferencia de inmunoglobulinas de la sangre al calostro al aumentar la actividad del receptor FcRn (Smith et al., 1971; Davis et al., 1979; Barrington et al., 2001). De hecho, se ha observado que vacas secas no gestantes tratadas con una combinación de estrógeno y progesterona pueden sintetizar un fluido con una composición similar al calostro (Smith et al., 1971), lo que sugiere que estas hormonas desempeñan un papel fundamental en la calostrogénesis, incluso en ausencia de gestación. El aumento de oxitocina antes del parto también induce el deterioro de las uniones estrechas entre las células epiteliales mamarias, mejorando la transferencia de ciertos componentes inmunes al calostro (Wall et al., 2016). Ciertamente, estas hormonas pueden regular la calostrogénesis a través de múltiples vías, no solo mediante la modulación de la actividad de los receptores, sino también a través de la activación de diferentes factores de transcripción en las células epiteliales mamarias (Topper y Freeman, 1980). De modo que, la compleja interacción entre hormonas, factores de transcripción, receptores, intermediarios intracelulares y moléculas de señalización extracelular es lo que probablemente

desencadena la síntesis del calostro (Groner, 2002; Akers, 2006). Antes del parto, el calostro se vuelve más líquido debido a un aumento de la cantidad de lactosa y agua (Davis et al., 1979; Bigler et al., 2023), que viene desencadenado por el incremento de la concentración de prolactina (Gross et al., 2014; Lacasse et al., 2016). La calostrogénesis cesará con el aumento de hormonas como la prostaglandina F2α (PGF2α) y la prolactina durante los últimos días de gestación marcando el comienzo de la lactogénesis II (Gross et al., 2014; Bigler et al., 2023). Por esta misma razón, la inducción del parto utilizando análogos de PGF2α puede ocasionar una reducción en la concentración de inmunoglobulinas en el calostro del ganado bovino, ovino y caprino (Field et al., 1989; Castro et al., 2011a). De manera similar, la administración de glucocorticoides entre las 6 y 8 semanas antes del parto en vacas lecheras cesa completamente la transferencia de IgG al calostro (Brandon et al., 1975).

2.2.5. COMPOSICIÓN DEL CALOSTRO

En función de las necesidades de la descendencia, los rumiantes han evolucionado para producir una secreción rica en nutrientes y compuestos bioactivos indispensables para garantizar una correcta termogénesis (Kirovski, 2015), así como un correcto desarrollo del sistema inmunitario (Stelwagen et al., 2009) y gastrointestinal (Roffler et al., 2003). La composición química y las propiedades inmunes del calostro pueden variar en función de la especie (Tabla 4), la raza, el número de lactación, la nutrición preparto, la duración del período seco, la salud de la ubre y la propia variabilidad individual (Caja et al., 2006; Zarcula et al., 2010; Kessler et al., 2019; Westhoff et al., 2024).

Uno de los estudios sobre la composición del calostro caprino fue desarrollado por Bergman y Turner (1936) quienes analizaron el calostro en busca de unos pocos constituyentes, incluyendo sólidos totales, grasa, caseína, albúmina, globulinas y cenizas. Recientemente, autores como McGrath et al. (2015), Playford y Weiser (2021) y Zhou et al. (2023) han recopilado los últimos datos sobre los componentes minoritarios presentes en el calostro bovino, ovino y caprino, y su impacto en el desarrollo fisiológico del neonato. De hecho, Hernández-Castellano et al. (2016), usando técnicas proteómicas, demostraron que el calostro de estas especies puede presentar diferencias significativas en múltiples componentes minoritarios. No obstante, el

conocimiento sobre los componentes bioactivos presentes en el calostro caprino sigue siendo muy limitado.

Tabla 4. Composición química y concentración de IgG en el calostro y leche de vacas, ovejas y cabras

Especie	Calostro				Leche			
	Lactosa (%)	Grasa (%)	Proteína (%)	IgG (mg/ml)	Lactosa (%)	Grasa (%)	Proteína (%)	IgG (mg/ml)
Vaca	1,9 - 3,0	6,7 - 7,0	11,7 - 31,6	40,3 - 61,9	4,4 - 5,6	3,3 - 5,4	3,7 - 3,9	0,6 - 0,9
Oveja	2,4 - 3,8	7,4 - 13,2	8,2 - 22,5	22,9 - 44,2	5,8 - 5,9	5,6 - 6,4	4,1 - 6,6	0,3 - 0,9
Cabra	2,0 - 4,4	4,0 - 8,0	10,6 - 17,1	26,6 - 41,1	4,2 - 4,3	3,8 - 4,3	4,4 - 4,5	0,7- 0,9

Fuente: Stelwagen et al. (2009); Galán-Malo et al. (2014); Alves et al. (2015); Hernández-Castellano et al. (2016); Kessler et al. (2019, 2020); Roy et al. (2020); Playford y Weiser (2021); Zarrin et al. (2021).

A continuación, se establece una clasificación simplificada de los componentes del calostro, segregando las moléculas con una función fundamentalmente nutritiva, de aquellos componentes bioactivos que se encuentran en menor concentración con capacidad de estimular el sistema inmune y el desarrollo gastrointestinal del neonato.

2.2.5.1. MACRONUTRIENTES Y MICRONUTRIENTES

La lactosa constituye el disacárido más abundante en el calostro y leche de los mamíferos. Su concentración en el calostro caprino oscila entre 2,0 - 4,4% (Tabla 4). Este disacárido es responsable de aproximadamente el 50% de la presión osmótica de la leche (McSweeney et al., 2009) y su secreción viene acompañada de un transporte de agua desde el citoplasma de las células epiteliales a la luz alveolar. Este hidrato de carbono evoluciona, al contrario que el resto de los componentes mayoritarios presentes en el calostro, pasando de unas bajas concentraciones en el primer ordeño a un incremento constante a medida que progresa la lactogénesis II. La menor concentración de lactosa en el calostro en comparación con la leche madura implica que éste tenga una consistencia más viscosa (Bleck et al., 2009).

Por otro lado, las proteínas son el nutriente más abundante en el calostro y la fuente principal de aminoácidos necesarios para la síntesis endógena de proteínas por parte del neonato (McGrath et al., 2015; Flavio et al., 2024). Aunque las proteínas más abundantes en el calostro son las caseínas (fracción insoluble), también existen otras en

menores concentraciones tales como las lactoglobulinas, albúmina, inmunoglobulinas, hormonas, enzimas y péptidos que forman parte del suero (fracción soluble), las cuales desempeñan un papel importante en el desarrollo del neonato (Hernández-Castellano et al., 2016). En el calostro caprino, se ha descrito una mayor proporción de β- y κ-caseínas y una menor proporción de α-caseínas con respecto a la leche madura (Quiles et al., 1991; Sun et al., 2019). Estas proteínas participan en el transporte de minerales y oligoelementos, y son capaces de reducir la degradación proteolítica al inhibir la acción de enzimas como la tripsina (Playford y Weiser, 2021). De acuerdo con varios estudios, la concentración de proteínas en el calostro caprino puede oscilar entre 10,6 - 17,1% en función de la raza (Tabla 5; Kessler et al., 2019; Agradi et al., 2023). También se ha descrito otro pequeño grupo de proteínas que forman parte de las membranas del glóbulo graso, las cuales se han relacionado con una actividad antimicrobiana y protección del tracto gastrointestinal (Patton y Keenan, 1995; Peterson et al., 1998).

Los lípidos son los segundos macronutrientes más importantes en el calostro y constituyen la principal fuente de energía para el recién nacido. También es el componente con mayor variabilidad oscilando entre 4,0 - 10,2% según la raza (Tabla 5). La fracción lipídica del calostro se compone de ácidos grasos poliinsaturados ω-3 y ω-6, ácido linoleico conjugado, ácidos grasos de cadena corta, gangliósidos y fosfolípidos (Playford y Weiser, 2021). La grasa presente en el calostro y la leche se encuentra casi en su totalidad en forma de glóbulos, es decir, triglicéridos situados en el interior de vesículas que se secretan por fusión con la membrana plasmática de la célula epitelial. Este proceso implica la adquisición de una bicapa lipídica denominada membrana del glóbulo graso, que contiene lípidos polares, colesterol y glicoproteínas, entre otros compuestos (Mather y Keenan, 1998). De hecho, varios estudios han demostrado que algunos componentes de la membrana del glóbulo graso (mucina-1 y la xantina deshidrogenasa/oxidasa) poseen la capacidad de inhibir la adhesión de patógenos a las células y tejidos intestinales, así como la de regular la señalización celular y la respuesta inmune (Reinhardt y Lippolis, 2008; Cebo et al., 2010; Douëllou et al., 2017).

En cuanto a los micronutrientes, el calostro contiene vitaminas liposolubles (A, D y E) e hidrosolubles (B) que poseen un papel fundamental en diversos procesos metabólicos, tales como el crecimiento óseo y la actividad antioxidante (Collins et al., 1952; Martin,

1997; Hodulová et al., 2015). Asimismo, algunas vitaminas, como la vitamina D, también se han relacionado con la modulación del sistema inmunitario (Aranow, 2011; Playford y Weiser, 2021). La mayoría de las vitaminas suelen presentarse en mayor concentración en el calostro en comparación con la leche madura, al igual que ocurre con diversos minerales como el calcio, el cobre, el hierro, el zinc, el magnesio, el manganeso y el fósforo (Valldecabrés y Silva-del-Río, 2022; Hare et al., 2023).

2.2.5.2. OTROS COMPONENTES BIOACTIVOS

A continuación, se describen los principales componentes bioactivos presentes en el calostro con un papel relevante en la protección y el desarrollo inmunitario del neonato.

a. COMPONENTES CON FUNCIÓN ANTIMICROBIANA E INMUNOMODULADORA

i. INMUNOGLOBULINAS

Las inmunoglobulinas son un componente fundamental del calostro, representando, aproximadamente, un tercio del total de las proteínas que lo componen (Rudovsky et al., 2008) y son consideradas como el principal indicador de la calidad del calostro. Estas proteínas pueden tener un origen humoral, adquiridas a través del torrente sanguíneo y/o un origen local, producidas por las células plasmáticas presentes en el tejido mamario (Larson et al., 1980). En los rumiantes, las inmunoglobulinas predominantes en el calostro son la IgG (≈ 90%), seguidas en menor concentración por la IgM (≈ 6%) y la IgA (≈ 4%; Rudovsky et al., 2008). Además, se han identificado dos subclases de IgG (IgG_1 e IgG_2), siendo la IgG_1 la más abundante, representando entre el 95-98% de la concentración total de IgG en el calostro de rumiantes (Micusan y Borduas, 1976).

Las inmunoglobulinas tienen un papel muy versátil en el organismo. Por un lado, previenen la adhesión de patógenos a las células del hospedador, presentan antígenos a los macrófagos y favorecen su eliminación confiriendo inmunidad pasiva al neonato, y por otro, estimulan la activación de linfocitos T y B, modifican la microbiota intestinal e inducen la producción local de otras inmunoglobulinas modulando el propio sistema inmune (Wheeler et al., 2007; Stelwagen et al., 2009).

ii. OLIGOSACÁRIDOS

Los oligosacáridos son carbohidratos de bajo peso molecular con función prebiótica y protectora (Martín-Sosa et al., 2003; Mcgrath et al., 2015). Éstos fueron descritos por primera vez en la leche humana y se dividen en dos grandes clases, neutros y ácidos. Los oligosacáridos neutros o galactooligosacáridos carecen de carga mientras que los oligosacáridos ácidos contienen uno o más residuos de N-acetilneuramínico (ácido siálico) que les confiere una carga negativa (Gopal y Gill, 2000).

Los oligosacáridos son capaces de mejorar la absorción de IgG (Gill et al., 1999) y servir como fuente de carbono para bacterias beneficiosas promoviendo su crecimiento en el intestino (Fischer-Tlustos et al., 2020). Además, pueden prevenir la adhesión bacteriana al actuar como sitios de unión para bacterias patógenas (*Escherichia coli, Salmonella* o *Helicobacter pylori*) asemejándose a los carbohidratos que constituyen la membrana de los enterocitos (Douëllou et al., 2017). Estudios recientes han demostrado que los oligosacáridos en el calostro caprino oscilan entre 200 y 650 mg/l en función de la raza y el número de partos (van Leeuwen et al., 2020) y disminuyen drásticamente durante los primeros 4 días postparto (Marziali et al., 2018).

iii. LACTOPEROXIDASA Y CHITOTRIOSIDASA

La lactoperoxidasa es una enzima oxidorreductasa secretada por las células epiteliales de la glándula mamaria, la cual desempeña un papel clave en la protección de ésta y del tracto intestinal del recién nacido (Naidu, 2000). Esta enzima cataliza la oxidación del tiocianato (SCN-) mediante el H_2O_2 y genera especies reactivas del oxígeno con propiedades antibacterianas. A pesar de haber sido ampliamente descrita, tan solo unos pocos trabajos han cuantificado esta enzima en el calostro caprino. Según Harjanti et al. (2017), la concentración de lactoperoxidasa en el calostro caprino es de 204 mg/l.

Por otro lado, la chitotriosidasa es una enzima sintetizada por macrófagos, capaz de hidrolizar la quitina presente en la pared celular de hongos y nematodos (Hollak et al., 1994; Renkema et al., 1995), así como de activar otras células inmunes (células T auxiliares y eosinófilos; Wiesner et al., 2015). Esta enzima tiene una mayor actividad en el calostro obtenido inmediatamente después del parto que en la leche de transición (3912 y 465 nmol/ml por hora, respectivamente) indicando su importancia en la

protección del neonato durante los primeros días de vida (Argüello et al., 2008; Castro et al., 2011a).

iv. LACTOFERRINA

La lactoferrina es una glicoproteína capaz de fijar iones férricos solubles con gran afinidad reduciendo su disponibilidad para el crecimiento bacteriano y fúngico. Es sintetizada por el epitelio de la glándula mamaria (Sánchez et al., 1992; Adlerova et al., 2008) y su concentración en el calostro caprino oscila entre 387 - 582 µg/ml (Hiss et al., 2008; Harjanti et al., 2017; Segura et al., 2024). Además, la lactoferrina se comporta como una proteína de fase aguda durante procesos inflamatorios e infecciosos (Kanyshkova et al., 2001) lo que también sugiere su participación en la respuesta inmune del organismo frente a diversos patógenos.

v. CITOQUINAS Y FACTORES DE CRECIMIENTO

Las citoquinas son péptidos sintetizados por leucocitos y células epiteliales que intervienen en la activación y el reclutamiento inmunitarios, la señalización celular y el reconocimiento de patógenos (Chae et al., 2017; Yazar y Bilgisi, 2023). Las citoquinas adquieren especial relevancia en momentos de estrés, inflamación o daño celular, estimulando la diferenciación celular, la quimiotaxis y la síntesis de proteínas. En el calostro y leche de cabra se han descrito diversas citoquinas como el interferón gamma (INF-γ) que participa en la activación de macrófagos, el factor de necrosis tumoral (TNFα) que interviene en la inflamación y la apoptosis celular, o las interleucinas (IL-2 y IL-5) que regulan la proliferación de células T o la activación, crecimiento y diferenciación de los linfocitos B (Isobe et al., 2020; Zhou et al., 2023). Asimismo, se han descrito factores de crecimiento, como el factor de crecimiento insulínico -1 y 2 que participan en la regulación de la hormona del crecimiento (Zhou et al., 2023). La presencia de estas moléculas en el calostro demuestra su importante papel en la modulación del desarrollo inmune y el crecimiento del neonato.

vi. EXOSOMAS

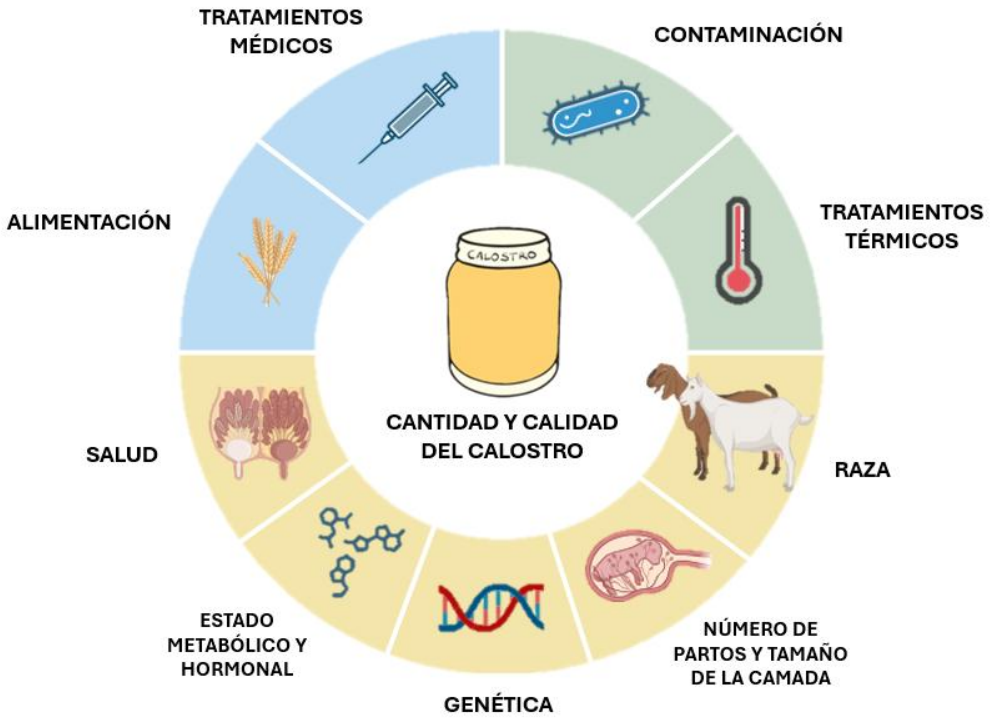
Los exosomas son vesículas extracelulares que se encuentran en diversos fluidos biológicos como la sangre, orina, saliva, calostro y leche entre otros (de la Torre-Gomez

et al., 2018; van Niel et al., 2018). Estas vesículas contienen gran variedad de moléculas tales como lípidos, proteínas o material genético (ADN y ARN; Yang et al., 2014; Rahmati et al., 2020). El calostro caprino contiene gran cantidad de exosomas y aunque sus funciones aún no están completamente definidas, estos compuestos pueden tener un papel clave en la modulación de las respuestas inflamatorias intestinales, la protección de la mucosa y la regulación de la expresión génica a nivel intestinal (Sedykh et al., 2020; Castro et al., 2024; Gao et al., 2024).

2.3. FACTORES QUE AFECTAN A LA PRODUCCIÓN Y COMPOSICIÓN DEL CALOSTRO

Los nutrientes y componentes bioactivos presentes en el calostro son vitales para asegurar la salud y el desarrollo del recién nacido. Su concentración depende de múltiples factores como la especie, la raza, el número de partos, la nutrición y el estado de salud de la madre, entre otros (Figura 4; Hernández-Castellano et al., 2016; Soufleri et al., 2021). A continuación, se detallan los factores intrínsecos y extrínsecos que pueden influenciar la composición del calostro en el ganado caprino.

Figura 4. Factores que afectan a la calidad del calostro



Fuente: Adaptado de Westhoff et al. (2024).

2.3.1. INTRÍNSECOS

a. GENOTIPO

Actualmente, la raza constituye el principal factor intrínseco determinante en la composición del calostro. La mayor parte de los estudios sobre la producción y composición del calostro caprino se han desarrollado de una manera muy individualizada. Razas caprinas como la Saanen o la Alpina han sido altamente seleccionadas para la producción láctea por lo que se utilizan fundamentalmente en sistemas de tipo intensivo. En regiones con menor grado de desarrollo y tecnificación del sector caprino lechero predominan las razas autóctonas, frecuentemente de aptitud mixta y mejor adaptadas a la escasez de recursos hídricos y forrajeros (Lu, 2023). Sin embargo, existe escasa información sobre la composición del calostro de razas locales y/o en peligro de extinción, ya que buena parte de estas ellas se mantienen en extensivo, lo que dificulta significativamente el acceso a los animales y la toma de muestras. No obstante, la preocupación por la conservación de las razas autóctonas y su papel en la conservación del medio natural ha despertado mayor interés en su estudio (Hernández-Castellano et al., 2016; Agradi et al., 2023). De hecho, Kessler et al. (2019) investigaron la composición del calostro (IgG, grasa, proteína y lactosa) en diez razas caprinas destinadas a la producción de leche y carne. En este trabajo se observó que la composición química del calostro varía enormemente entre razas, con concentraciones que varían entre el 1,3 y 16,5% para la grasa, el 4,9 y 25,1% para la proteína y el 2,1 y 6,0% para la lactosa. Con respecto a las concentraciones de IgG, también se ha observado una gran variabilidad (entre 4,8 y 75,0 mg/ml), siendo el calostro de razas cárnicas el que presenta mayor concentración de IgG. De manera similar, Agradi et al. (2023) evaluaron la composición del calostro en tres razas locales (Orobica, Lariana y Frisa) de tipo mixto en el norte de Italia y las comparó con una raza lechera cuyo uso está muy extendido en el norte de Italia (Camosciatta delle Alpi). Estos autores observaron una mayor concentración de IgG en el calostro de las razas locales con respecto a la raza de tipo lechero (100,90 ± 1,56 *vs*. 74,75 ± 4,12 mg/ml de IgG). Esta reducción de la concentración de componentes inmunes en el calostro de animales de alta producción había sido descrita previamente en el ganado bovino (Muller y Ellinger 1981; Zarcula et al., 2010). Sin embargo, existen ciertas discrepancias dado que algunos autores no han observado

las mismas diferencias (Kessler et al., 2020). No obstante, a pesar de una posible merma de la calidad, se sabe que las razas lecheras producen mayor volumen de calostro que las razas cárnicas (Hare et al., 2021) lo que puede causar una mayor dilución de los componentes inmunes del mismo.

Por otro lado, si bien la heredabilidad de la calidad del calostro aún debe explorarse en el ganado caprino, diversos estudios realizados en ganado bovino han demostrado la existencia de rasgos genéticos con mucho potencial para la mejora de la calidad de calostro. Gavin et al. (2018), Soufleri et al. (2019) y Cordero-Solorzano et al. (2022) encontraron que la concentración de IgG en el calostro tiene una heredabilidad moderada en vacas lecheras, oscilando entre 0,16 y 0,50 mientras que en razas cárnicas esta heredabilidad se sitúa en torno al 0,41. Esta correlación entre rasgos genéticos y la concentración de IgG en el calostro ofrece la oportunidad de mejorar la calidad del calostro mediante estrategias de selección genética. Incorporar este criterio en los programas de evaluación del ganado podría conducir a avances importantes en la producción de calostro de buena calidad.

b. NÚMERO DE PARTOS, TAMAÑO DE LA CAMADA Y SEXO DE LOS CABRITOS

El número de partos y el tamaño de la camada también se han asociado con algunos cambios en el rendimiento y la composición del calostro en cabras. Knight y Peaker, (1982) demostraron que la producción de calostro en las cabras multíparas es mayor que en las primíparas. De forma similar, Peris et al. (1999) demostraron que las cabras multíparas tienen mayor volumen de ubre y tejido secretor que las primíparas. Esto también se ha observado en vacas y ovejas lecheras (Fernandez et al., 1995; Walsh et al., 2007; Adegoke et al., 2016). Aunque Argüello et al. (2006) no describieron efectos del número de partos y el tamaño de la camada en el rendimiento y composición del calostro en cabras lecheras de raza Majorera, Romero et al. (2013) observaron mayores porcentajes de proteína y lactosa en el calostro de cabras de raza Murciano-Granadina, primíparas y de parto simple, sin efectos significativos en las concentraciones de inmunoglobulinas. Además, Zhou et al. (2023) descubrieron que las concentraciones de grasa, IgG, INF-γ e IL-2 en el calostro de las cabras de parto gemelar eran superiores a las de las cabras de parto simple. Estos resultados sugieren que el número de partos y el

tamaño de la camada pueden asociarse a modificaciones en el volumen de calostro y a una posible dilución de sus componentes.

Aunque no se ha descrito en ganado caprino, estudios realizados en ganado bovino han demostrado que el sexo de la cría también puede influir en el volumen de calostro, ya que las vacas lecheras que gestan terneras producen menos calostro que las que gestan terneros (Gavin et al., 2018; Borchardt et al., 2022; Westhoff et al., 2023). Es posible que esta relación se deba a la diferencia de tamaño entre terneros y terneras (Conneely et al., 2014). Asimismo, se ha observado que la gestación de gemelos aumenta la producción de calostro y que la ocurrencia de mortinatos se asocia con una menor producción de calostro (Borchardt et al., 2022; Westhoff et al., 2023).

2.3.2. EXTRÍNSECOS

a. SALUD DE LA UBRE

En 1971, Linzell y Peaker realizaron los primeros estudios sobre la permeabilidad de la glándula mamaria en cabras lecheras, indicando que las diferencias en la composición del calostro y la leche podrían ser causadas por cambios estructurales en los complejos de unión (desmosomas y uniones estrechas) entre las células epiteliales (Linzell y Peaker, 1971). Los mecanismos subyacentes a los cambios en la permeabilidad de la BMB son complejos y pueden estar asociados con cambios hormonales y metabólicos durante la gestación y la lactación.

Durante la mastitis o inflamación de la glándula mamaria, la BMB se vuelve permeable permitiendo el paso de células inmunes, como linfocitos y neutrófilos, de la sangre al lumen de alveolar (Burton y Erskine, 2003; Wellnitz y Bruckmaier, 2021). Las células inmunes reclutadas secretan IgG_1, IgG_2, IgM y citoquinas mejorando la fagocitosis de patógenos, lo que a su vez incrementa el recuento de células somáticas (SCC) en la leche (Wellnitz et al., 2015; Wall et al., 2018). Aunque, no se han detectado cambios en las concentraciones de inmunoglobulinas presentes en el calostro de vacas primíparas o multíparas con mastitis natural (Maunsell et al.,1998; Enger et al., 2021), sí que se ha observado un incremento de algunos componentes sanguíneos en la leche, como por ejemplo la albúmina sérica, LDH e IgG, tras inducir una mastitis experimental en vacas lecheras (Bruckmaier y Wellnitz 2017).

Algunos componentes de la pared celular como los lipopolisacáridos (LPS) de bacterias gram-negativas (*E. coli*), así como el ácido lipoteicoico o los peptidoglicanos de bacterias gram-positivas (*Staphylococcus aureus*) han sido ampliamente utilizados para reproducir una respuesta inmune similar a una mastitis en condiciones experimentales (Wellnitz et al., 2013; Kusebauch et al., 2018). Aunque la inflamación experimental se ha utilizado principalmente para evaluar la respuesta inmune local y determinar mejores enfoques para tratar las mastitis, algunos trabajos se han centrado evaluar su impacto en la composición de la leche y el calostro (Wellnitz y Bruckmaier, 2021). Danielsen et al. (2010) evaluaron el proteoma de la leche y la expresión génica durante la mastitis inducida en vacas lecheras (200 mg de *E. coli* serotipo O111:B4), observando un aumento de las proteínas de fase aguda, inmunoglobulinas y factores del complemento, así como un incremento de las α-, β- y k-caseínas tras 7 horas de exposición a los LPS. De forma similar, Salama et al. (2020) observaron mayores concentraciones de proteína y menores de lactosa en leche de cabras lecheras de la raza Murciano-Granadina tratadas con 10 µg de LPS intramamario (*E. coli* serotipo O55:B5). Estos hallazgos sugieren que la aplicación de LPS durante la lactación, y posiblemente durante la calostrogénesis, puede promover una mayor transferencia de nutrientes y componentes bioactivos mejorando la calidad de la secreción láctea. De hecho, una mayor permeabilidad de la BMB combinada con una vacunación frente a ciertos patógenos podría mejorar la transferencia de anticuerpos específicos de la sangre al calostro y a la leche, favoreciendo una mejor inmunización de la descendencia.

b. MANEJO NUTRICIONAL

El desarrollo de la glándula mamaria comienza antes del parto, un período en el que la captación de moléculas derivadas de la sangre aumenta progresivamente. En consecuencia, el aporte y la absorción de nutrientes durante el período seco puede afectar a la producción y composición del calostro (Hare et al., 2023). De hecho, una restricción de nutrientes durante la gestación causa una clara reducción en la producción de calostro tanto en vacas lecheras como en ovejas sin que ello afecte a la concentración de IgG (Logan, 1977; Banchero et al., 2006; Zarrin et al., 2021). Si bien los efectos de la restricción alimentaria en el calostro de cabra aún no se han evidenciado, se podría esperar una reducción similar. En cambio, se ha observado que el exceso de

los requerimientos energéticos en vacas lecheras durante la calostrogénesis no suele tener impacto sobre el volumen de calostro (Daneshvar et al., 2020; Fischer-Tlustos et al., 2021) ni sobre las concentraciones de IgG (Springer et al., 2008; Dunn et al., 2017), a pesar de que algunos autores sí han descrito una reducción de la concentración de IgG en el calostro de vacas alimentadas por encima de sus requerimientos nutricionales antes del parto (Mann et al., 2016). De manera similar, se ha observado que alimentar ovejas y cabras lecheras por encima de los requerimientos energéticos durante el último mes de gestación no afecta ni a la producción de calostro ni a la concentración de inmunoglobulinas (Celi et al., 2008; Gallo et al., 2020). Sin embargo, Ramírez-Vera et al. (2012) mostraron cómo cabras en pastoreo suplementadas con almidón de maíz 12 días antes del parto producen un mayor volumen de calostro y porcentaje de lactosa en el calostro. A pesar de todo, los datos disponibles en cabras lecheras en condiciones intensivas son escasos.

Por otro lado, la suplementación o la inclusión de diferentes fuentes de proteínas y grasas al final de la gestación no parece influir en la producción y la composición del calostro. Según Shabrandi et al. (2019), una suplementación preparto de hidratos de carbono y proteína metabolizable (PM) de manera simultánea puede causar un mayor desarrollo de la glándula mamaria en cabras lecheras sin afectar la producción del calostro. Resultados similares han sido observados en ovejas lecheras suplementadas con 116,5 g de proteína cruda (PC) y 84,6 g de PM/kg de materia seca (MS) en comparación con el grupo control que recibió 99,4 g de PC y 70,5 g de PM/kg de MS (Mousavi et al., 2016). Sin embargo, los resultados entre estudios siguen siendo inconsistentes, ya que algunos autores sí que han encontrado concentraciones más altas de proteínas en el calostro de ovejas después de la suplementación proteica durante la gestación (Amanlou et al., 2011). Las diferencias entre estudios podrían deberse a la fuente y el tipo de proteína (proteína degradable *vs*. proteína no degradable en el rumen) y la duración de la suplementación (3 *vs*. 6 semanas antes de la fecha de parto estimada). Asimismo, la suplementación de las dietas preparto con grasa también se ha evaluado. En vacas lecheras, la inclusión de diversas fuentes de grasa preparto aumenta las concentraciones de IgG y ácidos grasos en el calostro, pero no afecta a la producción (Ricks et al., 2020). A diferencia del ganado bovino, la suplementación con

ácido linoleico conjugado desde el tercer mes de gestación no aumenta la concentración de IgG en el calostro de cabras lecheras (Castro et al., 2006). De manera similar, Moreno-Indias et al. (2014) observaron que la suplementación con 5 g/día del alga *Chlorella pyrenoidosa* como fuente de ácidos grasos insaturados y aminoácidos esenciales (Chen et al., 2022; Kouřimská et al., 2014), no tiene ningún efecto sobre la producción, el perfil de ácidos grasos y los componentes inmunes en el calostro de cabras lecheras. Sin embargo, Cattaneo et al. (2006) describieron que la suplementación con 1,1% de aceite de pescado durante las últimas tres semanas antes del parto aumenta los ácidos grasos poliinsaturados de cadena larga n-3, principalmente ácido eicosapentaenoico y docosahexaenoico, en el calostro de cabras lecheras. En ovejas, la suplementación con aceite de pescado durante el período seco tiene un impacto negativo en la producción de calostro, así como en las concentraciones de grasa, proteína e IgG (Annett et al., 2009). De manera general, las diferencias observadas entre los estudios podrían estar asociadas con factores como la fuente de los nutrientes suplementados, el momento y la duración de la suplementación, la raza y el sistema de manejo ya que estos pueden influir directamente en la magnitud de la respuesta a la suplementación.

2.4. DESARROLLO DEL CABRITO NEONATO

La transición entre la vida *in utero* y la *ex utero* requiere de importantes adaptaciones metabólicas, hormonales e inmunológicas en los rumiantes. La nutrición, y en especial la ingestión de calostro en las primeras horas de vida tendrá efectos en el rendimiento productivo, la salud y el bienestar a corto y largo plazo (Blum y Hammon, 2000).

2.4.1. TRANSFERENCIA DE INMUNIDAD PASIVA

Según Carter y Mess, (2017), Auad et al. (2019) y Bigler et al. (2022) la estructura de la placenta epiteliocorial en los ungulados impide la transferencia de componentes inmunes de la madre al feto. Por este motivo, los cabritos neonatos, al igual que los terneros y corderos, son considerados hipo – o agammaglobulinémicos al nacimiento, por lo que la concentración de inmunoglobulinas en sangre es muy baja e incluso, en algunos casos, indetectable antes de la toma de calostro (Constant et al., 1994; Argüello et al., 2004c; Castro et al., 2005).

De acuerdo con estudios previos, los cabritos neonatos deben recibir al menos 4 gramos de IgG por kilo de peso vivo al nacimiento, durante las primeras 24 horas de vida para garantizar una correcta TPI, consiguiéndose así concentraciones plasmáticas superiores a los 11,4 mg/ml de IgG (Rodríguez et al., 2009; Zamuner et al., 2023). De hecho, según Argüello et al. (2004c) y Castro et al. (2005), la concentración de IgG en el plasma sanguíneo de cabritos neonatos está altamente correlacionada con la concentración de IgG consumida en las primeras 72 horas de vida. Tras este período, los niveles de IgG de origen materno comienzan a disminuir a la vez que comienza la síntesis endógena de inmunoglobulinas en el propio cabrito, la cual tiene lugar entre las 2 a 3 semanas de edad, alcanzando concentraciones normales de adulto alrededor de las 10 - 12 semanas de vida (Micusan et al., 1976; Argüello et al., 2004c). Sin embargo, se ha observado que los terneros alimentados con una cantidad insuficiente de calostro comienzan a producir anticuerpos de forma más temprana (Barrington y Parish, 2001). Durante este vacío de inmunidad que tiene lugar cuando las IgG adquiridas pasivamente a través del calostro alcanzan su concentración más baja y antes de la producción endógena, los rumiantes neonatos son más susceptibles a enfermedades (Husband y Lascelles, 1975).

a. MANEJO DEL ENCALOSTRADO

Las prácticas de encalostrado más frecuentes en la ganadería caprina incluyen el encalostrado natural y el encalostrado artificial con calostro fresco, refrigerado y/o congelado. El encalostrado artificial implica la separación de los cabritos de sus madres y el aporte de un volumen de calostro equivalente al 10% del peso vivo al nacimiento dividido en dos tomas durante las primeras 24 horas de vida (Argüello et al., 2004c). En algunas regiones donde la prevalencia de enfermedades que pueden trasmitirse a la decendencia a través del calostro, tales como el virus de la artritis encefalitis caprina y la paratuberculosis, se recurre frecuentemente a la pasteurización. No obstante, se ha demostrado que este tratamiento térmico reduce hasta un 35% la concentración de IgG en el calostro caprino (Arguello et al., 2003), por lo que se recomienda usar calostro de alta calidad para asegurar una correcta TPI tras la pasteurización. Como alternativa a los tratamientos térmicos, algunos productores recurren al uso de calostro reemplazantes comerciales para evitar la transmisión vertical de estas enfermedades (Bélanger-Naud y Vasseur, 2021; Graydon et al., 2024) y facilitar el manejo del encalostrado. Según Jones

et al. (2004), no existen diferencias en la concentración de IgG plasmática a las 24 horas de vida en terneros alimentados con calostro materno (13,78 ± 0,39 g/l) o con un calostro reemplazante (13,96 ± 0,38 g/l). Aunque varios autores coinciden con los resultados descritos anteriormente, Lopez et al. (2020) y Silva et al. (2020) publicaron resultados opuestos, encontrando animales con fallos de TPI cuando reciben este tipo de reemplazantes (Smith y Foster, 2007). Por otro lado, se ha demostrado que el encalostrado de corderos recién nacidos con calostro de origen caprino asegura una correcta inmunidad pasiva (Hernández-Castellano et al. 2015). Sin embargo, Zadoks et al. (2001) y Argüello et al. (2004) observaron que los cabritos alimentados con calostro reemplazantes de origen bovino y ovino, respectivamente, presentaban concentraciones plasmáticas de IgG no detectables o inferiores a los que recibieron calostro materno a las 24 horas de vida, evidenciando, en ambos casos, un fallo en la TPI. Las discrepancias entre estudios pueden deberse, a la formulación de los calostro reemplazantes (derivados de suero bovino, calostro bovino u ovino liofilizado), los protocolos de encalostrado (1 *vs*. 2 tomas; gramos de IgG/kg de peso vivo o el intervalo de tiempo entre tomas) o a las técnicas utilizadas para determinar la concentración de estas inmunoglobulinas. La escasa literatura disponible y la ineficacia de los calostro reemplazantes revela la necesidad de profundizar en el estudio de la composición del calostro y el papel de los anticuerpos heterólogos como alternativas eficaces para garantizar una correcta transferencia de inmunidad en los rumiantes.

b. ABSORCIÓN INTESTINAL

La adquisición de una correcta inmunidad pasiva en los rumiantes está directamente relacionada con la capacidad de absorción intestinal. Durante las primeras horas de vida, la permeabilidad intestinal permite la absorción inespecífica de macromoléculas presentes en el calostro (Bangham et al., 1958; Jochims et al., 1994). Según Comline et al. (1951) los componentes del calostro absorbidos por el epitelio intestinal de un rumiante recién nacido se incorporan a través del sistema linfático y posteriormente ingresan en la circulación sistémica mediante el conducto torácico. Asimismo, la absorción de estos componentes se ve favorecida por una baja actividad proteolítica en el tracto gastrointestinal del neonato (Guilloteau et al., 1983) y a la presencia de α1-antitripsina en el calostro (Quigley et al., 1995).

Diversos estudios han demostrado que la absorción de los componentes calostrales, especialmente las inmunoglobulinas, tiene lugar mediante un mecanismo de pinocitosis a lo largo del intestino delgado (Stott et al., 1979, Fischer-Tlustos et al., 2021; Figura 6). Aunque aún existe cierta controversia y se desconocen los mecanismos que dirigen este transporte, algunos estudios también han demostrado la existencia de receptores de tipo Fc (fragmento cristalizable) en el intestino de ratas, humanos, cerdos y terneros (Simister y Rees, 1985; Sha et al., 2003; Cabrera et al., 2013) indicando un posible transporte selectivo de estas moléculas hacia el interior de los enterocitos.

La primera ingestión de calostro desencadena una importante remodelación de la mucosa intestinal en el neonato. La proliferación y muerte celular de la mucosa intestinal están bajo el control directo de múltiples factores de crecimiento (EGF, IGFs, TGF-βs) y hormonas (leptina, ghrelina, etc.) presentes en el calostro y/o producidas por el propio tracto digestivo del recién nacido (Godlewski, 2011). De este modo, el calostro es capaz de inducir una apoptosis celular a nivel intestinal facilitando la eliminación de enterocitos de tipo fetal y el cierre de la barrera intestinal (Blättler et al., 2001; Godlewski, 2011). De hecho, Castro-Alonso et al. (2008) demostraron un incremento de la apoptosis intestinal en cabritos neonatos de forma paralela a una disminución de la absorción de IgG durante los primeros días de vida.

Por otro lado, algunos autores han descrito una posible saturación de la absorción de componentes durante este período en el que el intestino es más permeable. Este concepto fue sugerido por primera vez por Besser et al. (1985), quienes afirmaron que los terneros podrían tener una limitación fisiológica para la absorción de IgG en función de la concentración de calostro ingerida. De acuerdo con Saldana et al. (2019), la eficacia aparente de absorción de IgG es mayor en aquellos terneros que reciben calostro de calidad media (65,7 ± 0,84 mg/ml; 38,1% eficacia aparente de absorción, AEA) en comparación con los alimentados con calostro de alta calidad (98,1 ± 0,84 mg/ml; 25% AEA). Estos resultados coinciden con Conneely et al. (2014), quienes también sugieren que puede existir un límite de absorción intestinal ya que los terneros alimentados con una cantidad de calostro equivalente al 8,5% de su peso corporal parecen alcanzar una mayor concentración de IgG plasmática durante los tres primeros días de vida en comparación con los terneros alimentados con cantidades equivalentes

al 7 o al 10% de su peso corporal. En cambio, aunque Rodríguez et al. (2009) no encontraron diferencias en la concentración plasmática de IgG en cabritos cuando se les alimenta con calostros que contienen diferentes concentraciones de IgG (20, 40, 60 y 80 mg/ml), sí que observaron un aumento de la eficacia aparente de absorción en aquellos cabritos que reciben calostro más concentrado (80 mg/ml de IgG). Todo esto puede indicar que parte de la IgG presente en el calostro no es absorbida, sino que actúa en el lumen intestinal y/o se elimina a través de las heces (Matte et al., 1982). Asimismo, Gelsinger et al. (2015) y Saldana et al. (2019) demostraron que la eficacia aparente de absorción de IgG mejora como resultado de una reducción de la carga bacteriana del calostro, de manera que la calidad microbiológica del calostro también constituye uno de los factores capaces de interferir en la absorción intestinal.

Tabla 3. Composición química y compuestos bioactivos cuantificados en el calostro caprino

Raza	Composición química			Componentes bioactivos				Referencia bibliográfica
	Lactosa (%)	Proteína (%)	Grasa (%)	IgG (mg/ml)	Lactoferrina (µg/ml)	IGF-1 (ng/ml)	3'SL (µg/ml)	
Aptitud lechera								
Saanen	3,6 ± 0,73	14,0 ± 5,27	6,6 ± 3,45	43,8 ± 20,7	1534,33 ± 10,79	422,27 ± 12,05	105,12 ± 3,23	Kessler et al. (2019); Yufang et al. (2021); Zhang et al. (2023)
Toggenburg	3,6 ± 0,50	13,2 ± 3,09	7,0 ± 2,35	39,4 ± 16,2	-	-	142,1 ± 2,03	Kessler et al. (2019)
Camosciata Delle Alpi	2,5 ± 0,12	14,2 ± 0,59	6,9 ± 0,53	74,8 ± 4,12	763,1 ± 76,31	-	-	Agradi et al. (2023)
Anglo-Nubia	3,2 ± 0,62	16,4 ± 4,69	4,0 ± 1,64	47,7 ± 17,0	-	-	-	Kessler et al. (2019)
Murciano-Granadina	2,5 ± 0,11	10,4 ± 0,23	9,4 ± 0,08	30,3 ± 7,90	-	-	-	Marzali et al. (2018)
Majorera	2,0 ± 0,75	10,2 ± 1,56	9,1 ± 3,30	41,1 ± 5,65	-	-	-	Hernández-Castellano et al. (2016)
Aptitud cárnica								
Boer	3,6 ± 0,41	17,1 ± 1,01	4,38 ± 1,35	61,0 ± 10,3	-	-	-	Kessler et al. (2019)
Aptitud mixta								
Orobica	3,2 ± 0,17	10,8 ± 1,07	7,1 ± 0,59	80,3 ± 5,57	1132,4 ± 153,08	-	-	Agradi et al. (2023)
Lariana	1,9 ± 0,17	16,2 ± 0,72	10,2 ± 0,66	93,1 ± 2,71	1148,0 ± 179,03	-	-	Agradi et al. (2023)
Frisa	2,4 ± 0,16	15,4 ± 0,81	8,3 ± 0,52	100,9 ± 1,56	1781,3 ± 168,69	-	-	Agradi et al. (2023)

Abreviaciones: IgG = Inmunoglobulina G; IGF-1 = Factor de crecimiento similar a insulina 1; 3'-SL = 3'-siali-lactosa.

Anexo

English Summary

1. NEONATAL MORTALITY AND THE IMPORTANCE OF COLOSTRUM

Neonatal mortality is closely associated to insufficient colostrum intake or poor-quality colostrum. This issue stands as one of the main reasons for reduced performance and welfare in dairy goat farms. As reported by several studies, goat kid mortality before weaning ranges within 4.3 and 57.7% (Table 1). According to Bajhau and Kennedy (1990) and Argüello et al. (2004a), most losses occur within the first days of life and when birth body weight is below 2.5 kg.

Colostrum contains nutrients and other components that are essential for thermogenesis, growth and development of the neonate during the first days of life (Bergman et al., 1937; Stelwagen et al., 2009). It contains bioactive molecules (i.e., immunoglobulins, oligosaccharides, peptides, enzymes, hormones and exosomes) that can be absorbed or have a local function within the gut (Wheeler et al., 2000; Kargar et al., 2020). Most components present in colostrum reach the secretion through active transport mechanisms, endo- and exocytosis, or through passive diffusion through the epithelial cells (Wheeler et al., 2007; Wall et al., 2015). While the concentration of these components is influenced by multiple factors such as species, breed, nutrition, and health of the dam (Hernández-Castellano et al., 2016; Soufleri et al., 2021), the specific mechanisms that regulate the synthesis and origin of some of these components are still unknown (Aitken et al., 2011; Baumrucker et al., 2021). Colostrum quality can be primarily determined by its immunoglobulin G (IgG) concentration, which can be measured using laboratory techniques such as radioimmunoassay (RIA), radial immunodiffusion (RID), or enzyme-linked immunosorbent assay (ELISA; Weaver et al., 2000). In addition, optical or digital refractometry has become a popular on-farm tool to estimate colostrum quality (Castro et al., 2018; Pérez-Marín et al., 2023).

2. LATE GESTATION PHYSIOLOGY AND COLOSTRUM MODULATION

Several metabolic and hormonal changes take place during late gestation related to fetal growth and mammary gland development (Bell et al., 1997; de Souza Castagnino et al., 2015). The increased energy demand in high yielding animals with high prolificacy results in a greater negative energy balance (NEB) which involves the intensification of certain metabolic pathways (Zamuner et al., 2020). At the same time, it can be observed a

progressive decline in progesterone levels that comes with the increase of estrogens, oxytocin, prostaglandin F2α, and cortisol concentrations resulting on the onset of parturition (Henricks et al., 1972; Bigler et al., 2023). This will be followed by increased prolactin concentrations which will be responsible for maintaining lactation (Grattan et al., 2008).

Additionally, the development of the mammary gland during late gestation is associated with multiple changes such as proliferation, apoptosis, cell differentiation, as well as changes in gene expression (Knight and Peaker 1982; Hou et al., 2017). Histologically, the alveoli consist of a basement membrane where the epithelial, endothelial and myoepithelial cells are located (Cowie et al., 1952; Howe et al., 1975). This structure is known as the blood-milk barrier (BMB; Bruckmaier & Wellnitz, 2017) and regulates the exchange of molecules between the blood and the alveolar lumen (Wheeler et al., 2007). Despite tight junction regulation around parturition is still not well understood, the increased permeability of the BMB in the last weeks of gestation can promote the paracellular transport of nutrients, bioactive molecules, and immune cells from blood to colostrum (Nguyen and Neville, 1998). Yet, it has been demonstrated that the permeability of the BMB can be modified by hormones such as glucocorticoids (i.e., dexamethasone, prednisolone, cortisol), oxytocin, or progesterone, as well as by bacteria and its toxins (i.e., lipopolysaccharides, lipoteichoic acid, or peptidoglycan) inducing changes in milk composition (Wellnitz and Bruckmaier, 2021). In addition, other studies have demonstrated that dry-off strategies and nutritional management during the dry period can result in changes in colostrum yield and quality in cattle (Gulliksen et al., 2008; Nowak et al., 2012), sheep (Banchero et al., 2004a, 2004b; Zarrin et al., 2021), and goats (Castro et al., 2011; Caja et al., 2006).

3. TRANSFER OF PASSIVE IMMUNITY

The placental structure of ungulates (i.e., epitheliochorial; Robertson et al., 2020) does not allow the transfer of immune components from dam to fetus, resulting in hypo- or agammaglobulinemic newborns. Therefore, colostrum is responsible for the proper transfer of passive immunity (TPI; ≥ 11.4 mg/mL of IgG in serum; Zamuner et al., 2023). In order to promote a successful TPI, a good colostrum quality must be fed shortly after birth to the newborn goat kid (i.e., ≥ 20 mg/mL of IgG; Argüello et al., 2005) as the gut

permeability decreases rapidly (Castro-Alonso et al., 2008; Moretti et al., 2012, 2013). During the first hours of life, the intestinal permeability allows a non-specific absorption of macromolecules which will be followed by a progressive replacement of fetal enterocytes, resulting in the gut closure (Bangham et al., 1958; Jochims et al., 1994; Blättler et al., 2001; Godlewski, 2011). While some studies have demonstrated the presence of intestinal Fc (crystallizable fragment) receptors suggesting a possible selective transport into enterocytes (Simister and Rees, 1985; Sha et al., 2003; Cabrera et al., 2013), some authors have demonstrated that there might be also a physiological limitation to absorb IgG (Besser et al., 1985; Saldana et al., 2019). In fact, Rodriguez et al. (2009) demonstrated that goat kids receiving colostrum with different IgG concentrations (i.e., 20, 40, 60, 80 mg/mL) did not showed differences in plasma IgG concentration 24 hours after colostrum intake. Colostrum management practices in intensive dairy goat farms frequently requires an artificial rearing of goat kids. This practice involves administering a colostrum amount equivalent to 10% of the birth body weight in two feedings within 24 hours of life to ensure a correct TPI (Rodríguez et al., 2009; Argüello et al., 2004c). Pasteurization is used in regions with high prevalence of certain diseases, although it reduces colostrum IgG concentration (Arguello et al., 2003). Despite, commercial colostrum replacers are often used as an alternative to avoid vertical disease transmission and to simplify management, some studies have reported failures in the TPI (Smith y Foster, 2007; Graydon et al., 2024).

Hipótesis

Hypotheses

HIPÓTESIS

En la presente Tesis Doctoral se hipotetizó que 1) el aumento del contenido de almidón en la dieta durante el último mes de gestación de las cabras lecheras incrementa la cantidad de calostro producido, así como mejora la composición de éste; 2) el aumento del contenido de almidón en la dieta durante el último mes de gestación mejora el metabolismo y la inmunidad adquirida en los cabritos durante el primer mes de vida; 3) la administración intramamaria de lipopolisacáridos bacterianos en el momento del parto permite modular la permeabilidad de la barrera sangre-leche mejorando la composición del calostro de cabras lecheras; 4) la administración intramamaria de lipopolisacáridos bacterianos en el momento del parto favorece la transferencia de inmunidad pasiva y el rendimiento en los cabritos durante el primer mes de vida; 5) las expresiones faciales pueden ser usadas para evaluar el dolor o malestar en los cabritos lactantes.

HYPOTHESES

This PhD thesis hypothesizes that 1) increased dietary starch content during the last month of gestation increases colostrum yield and enhances colostrum composition in dairy goats; 2) increased dietary starch content during the last month of gestation improves performance and acquired immunity in goat kids during the first month of life; 3) the intramammary administration of lipopolysaccharides at parturition modulates the permeability of the blood-milk barrier improving colostrum composition in dairy goats; 4) the intramammary administration of lipopolysaccharides at parturition enhances the transfer of passive immunity and performance in goat kids during the first month of life; 5) facial expressions can be used to assess pain or discomfort in goat kids.

Objetivos

Objectives

OBJETIVOS

El objetivo general de la presente Tesis Doctoral fue el estudio de nuevas estrategias de manejo a través de modificaciones en la dieta y la aplicación de moléculas vía intramamaria durante la calostrogénesis para mejorar la cantidad de calostro producido, así como la calidad de éste en ganado caprino y, por ende, mejorar la inmunidad adquirida en cabritos. Como objetivos específicos se establecieron:

1. Revisar los procesos fisiológicos involucrados en la calostrogénesis de los rumiantes, con especial interés en el ganado caprino, y examinar diversas estrategias de manejo con capacidad de modular la síntesis del calostro en esta especie (Capítulo 3).
2. Evaluar el efecto del incremento del contenido de almidón en la dieta preparto de cabras lecheras sobre la cantidad y calidad de calostro, el estado inmune y metabólico de las cabras desde el último mes de gestación hasta el primer mes postparto, así como sobre el crecimiento, estado inmune y metabólico de los cabritos durante el primer mes de vida (Capítulo 4).
3. Evaluar el efecto de la administración intramamaria de lipopolisacáridos (LPS) a cabras lecheras en el momento del parto sobre la cantidad y calidad del calostro, así como sobre el estado inmune y metabólico durante el primer mes postparto (Capítulo 5).
4. Evaluar el efecto de la administración intramamaria de lipopolisacáridos (LPS) en cabras lecheras en el momento del parto sobre el crecimiento, el estado inmune y metabólico de los cabritos durante el primer mes de vida (Capítulo 6).
5. Evaluar las expresiones faciales como indicadores potenciales de dolor y malestar en cabritos lactantes durante el primer mes de vida (Capítulo 7).

OBJECTIVES

The main objective of this PhD thesis was to study new management strategies through dietary modifications and the application of intramammary molecules during colostrogenesis to improve colostrum quality in goats and the transfer of passive immunity in goat kids. The specific objectives were:

1. To review the metabolic and hormonal mechanisms regulating colostrogenesis in dairy ruminants, with special focus on dairy goats, to evidence different management strategies that could be used to manipulate colostrum synthesis in this species (Chapter 3).
2. To evaluate the effect of a high-starch diet prepartum on colostrum yield and quality, immune and metabolic status of dairy goats before and after parturition as well as on goat kid performance and immune and metabolic status during the first month of life (Chapter 4).
3. To evaluate the effect of the intramammary administration of lipopolysaccharides (LPS) on dairy goats at parturition on colostrum yield and quality as well as on the immune and metabolic status during the first month postpartum (Chapter 5).
4. To evaluate the effect of the intramammary administration of lipopolysaccharide (LPS) to dairy goats at parturition on performance as well as immune and metabolic status of goat kids during the first month of life (Chapter 6).
5. To evaluate facial expressions as potential indicators of pain and discomfort in pre-weaned goat kids (Chapter 7).

Capítulo 3

Chapter 3

Fisiología y modulación de la glándula mamaria durante la calostrogénesis en cabras lecheras

Mammary gland physiology and modulation during colostrogenesis in dairy goats

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RESUMEN

La calostrogénesis implica varios mecanismos fisiológicos que resultan en una mezcla compleja de nutrientes y componentes bioactivos directamente involucrados en la supervivencia del recién nacido. La síntesis del calostro parece estar esencialmente regulada por el sistema neuroendocrino. No obstante, distintas prácticas de manejo durante el período de secado, así como el período seco, tales como la inclusión de diferentes nutrientes en las dietas preparto y la respuesta inmune de la glándula mamaria durante la inflamación pueden influir el desarrollo de la calostrogénesis y, en consecuencia, usarse estratégicamente para mejorar la calidad del calostro. La combinación de distintas frecuencias de ordeño o diferentes niveles energéticos en la dieta durante el período de secado, unido a un período seco con una duración de dos meses previos al parto, o una suplementación nutricional controlada durante el último mes de gestación puede promover la adecuada involución y regeneración de la glándula mamaria, así como inducir cambios metabólicos que promuevan la síntesis del calostro. Si bien se han descrito múltiples efectos sobre el metabolismo, la literatura actual demuestra que la composición del calostro en cabras lecheras parece no responder a la suplementación con hidratos de carbono, proteínas y grasa antes del parto. Sin embargo, es necesario aún evaluar nuevas pautas de alimentación tales como la duración, la proporción y la fuente del nutriente utilizado para desarrollar mejores estrategias nutricionales que permitan modular y promover el rendimiento y la composición del calostro en la especie caprina. Por otro lado, es evidente que la inflamación de la glándula mamaria de origen infeccioso tiene efectos negativos en la salud del animal, sin embargo, se ha demostrado que la inflamación inducida experimentalmente desencadena modificaciones en la barrera sangre-leche, pudiendo influir en la composición química e inmune de la leche y el calostro. El futuro de la modulación de la calostrogénesis deberá centrarse en desarrollar nuevas estrategias de manejo durante el período de secado, evaluar los efectos de un manejo nutricional preciso y una estimulación controlada de la respuesta inmune local al final de la gestación con el fin de promover la cantidad y calidad del calostro y, en consecuencia, la salud y el crecimiento de los cabritos.

Mammary gland physiology and modulation during colostrogenesis in dairy goats.

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Abstract

Newborn ruminants are highly dependent on the intake of high-quality colostrum immediately after birth to obtain energy and achieve an appropriate immunization. Previous research indicates that poor management practices in the last months of gestation can lead to increased neonatal mortality rates by reducing colostrum quality among other factors. In ruminants, colostrum synthesis is a well-preserved mechanism which seems to be essentially regulated by the neuroendocrine system. However, this review explores different approaches such as different dry-off management practices, the inclusion of different nutrients on prepartum diets, and the stimulation of the mammary gland immune response to modulate colostrogenesis and consequently, to enhance colostrum quality. Ensuring correct dry-off practices combined with controlled dietary supplementation can support mammary gland reorganization and potentially modulate colostrogenesis. Despite positive effects on colostrum yield, the bioactive composition of colostrum seems to be irresponsive to prepartum energy, protein, and fat supplementation in dairy goats. On the other hand, mastitis has obvious negative effects on animal health; however, an experimental induced inflammation seems to trigger helpful modifications on the blood-milk barrier, enhancing the concentration of some immune components (i.e., IgG and IgM) in goat colostrum. Yet, most research has focused on dairy cattle, leaving a significant knowledge gap on colostrogenesis in small ruminants. Therefore, future studies should focus on developing novel dry-off and dietary strategies to not only promote a healthy lactation but also to guarantee a successful colostrum synthesis.

Keywords: small ruminant, dry period, management, physiology, inflammation

Implications

The omission of the dry period reduces colostrum yield and quality. Newer approaches based on reducing energy supply, milking frequency or applying melatonin implants during dry-off, the starch supplementation during the last month of gestation or the intramammary administration of low doses of lipopolysaccharides at parturition seem to be effective strategies to enhance colostrum quality and yield. Increased colostrum quality will improve the transfer of passive immunity from dams to newborn ruminants, increasing the health status and performance of the offspring, which in turn will promote a better performance in their adult life.

Introduction

The dairy goat industry faces important challenges such as reduced feed sources and pastures caused by droughts, the rise of feed prices or the widespread infectious diseases. All these aspects have considerable negative effects on animal performance. However, dairy goat producers have also identified neonatal mortality as a major economic and welfare issue (Rätsep, 2020). Goat kid mortality within the first week of life is commonly associated with the presence of pneumonia, diarrhea, or starvation among other health issues. Despite the timing of kid mortality still not being well-defined, most losses have been observed in animals with birth BW < 2.5 kg and within the first days of life (Bajhau and Kennedy, 1990), as those animals often show reduced blood immunoglobulins concentrations within the first 84 h of life (Zamuner et al., 2023; Argüello et al., 2004). Consequently, these animals have greater susceptibility to infections, which in turn increases mortality rates. Several studies reported preweaning goat kid mortality across the world ranging within 4.3% and 57.7% (Table 1). This mortality rate is highly influenced by multiple factors such as management system, dam health, birth body weight, litter size, season (i.e., low ambient temperatures), and successful immunization after colostrum intake (Chowdhury et al., 2002; Mota-Rojas et al., 2022; Perez-Razo et al., 1998; Robertson et al., 2020). However, literature regarding neonatal mortality in the dairy goat sector across Europe is scarce, making it difficult to assess and compare results among countries.

Unlike other mammals, ruminants do not transfer enough maternal immune components to their offspring during gestation (Bigler et al., 2022; Green et al., 2021). As a result, newborn ruminants are strictly dependent on colostrum intake, not only as a source of nutrition, but also for acquiring essential immune components. In addition, it is crucial that colostrum is provided within the first hours of life (Castro-Alonso et al., 2008; Moretti et al., 2012, 2013) as the apoptotic activity of enterocytes rapidly decreases, reducing the intestinal ability to absorb large molecules such as immunoglobulins. Additionally, enterocytes proliferation and apoptosis are regulated by growth factors (i.e., EGF, IGFs, TGF-βs) and hormones (i.e., leptin, ghrelin) present in colostrum (Godlewski, 2011) proving its role in the gut closure. Colostrum also contains essential nutrients such as lactose and triglycerides that can be metabolized to produce energy and induce thermogenesis. Indeed, it has been demonstrated that rectal temperature in newborn calves increases within the first hours after colostrum consumption contributing to their survival under harsh environmental conditions (Kirovski, 2015).

Colostrum also provides diverse bioactive molecules (i.e., immunoglobulins, growing factors, peptides, enzymes and hormones) which are either absorbed or act within the gut lumen during the first hours of life. These components are vital to ensure newborn survival, and its concentration depends on multiple factors such as species, breed, dam nutrition, and health status (Hernández-Castellano et al., 2016; Soufleri et al., 2021). Besides its effects on passive immunity, colostrum also promotes gastrointestinal tract development and health of newborn ruminants. According to Kargar et al. (2020) and McCarthy et al. (2024) an extended colostrum feeding during the first two weeks of life can increase daily weight gain and reduce diarrhea and pneumonia susceptibility in dairy calves, whereas these effects in goat kids still need to be addressed. This time-sensitive process underlines the vital role of prompt colostrum intake to ensure the health status of newborn ruminants.

As colostrum is one of the main factors affecting goat kid mortality, several studies have been conducted to define its quality. Colostrum quality can be primarily determined by its immunoglobulin G (IgG) concentration, which is considered the main parameter responsible for a correct transfer of passive immunity (TPI). Literature describes several techniques used to measure IgG concentration in colostrum, including laboratory assays such as radioimmunoassay (RIA), electrophoresis, radial immunodiffusion (RID), and enzyme-linked immunosorbent assay (ELISA; Weaver et al., 2000). Additionally, on-farm practical estimation methods such as colostrometers (Bartier et al., 2015), optical or digital refractometers (Castro et al., 2018; Pérez-Marín et al., 2023) and visual color assessments (Argüello et al., 2005) are also available. These approaches provide both, precise analyses and accessible on-farm tools enabling researchers and farmers to effectively evaluate colostrum quality.

Despite most colostrum research on dairy ruminants has been performed on dairy cows, there is no clear definition of colostrum quality in this species as it differs significantly between species and breeds (Nowak and Poindron, 2006; Stelwagen et al., 2009; Wheeler et al., 2007). A similar situation has been showed on colostrum research performed on dairy goats (Agradi et al., 2023; E. Kessler et al., 2019; Torres et al., 2013). Currently, cut-offs values to define good quality colostrum have been set as ≥ 50 mg/mL of IgG in cattle (Weaver et al., 2000), and ≥ 20 mg/mL of IgG in goats (Argüello et al., 2005; Castro et al., 2005; Kessler et al., 2021). Yet, no cut-off values have been stablished for sheep colostrum IgG concentration. Defining clear thresholds, analogous to those in dairy cattle has become essential for improving colostrum management practices in small ruminants, which have been reviewed by (Castro et al., (2011b) and Fischer-Tlustos et al. (2021). In calves, IgG and serum total protein concentrations ≥ 10mg/mL and ≥ 6.2 g/dL, respectively, and ≥ 15 mg/mL and ≥ 4.6 g/dL in lambs and goat kids have been widely accepted as cut-offs values for successful passive transfer of immunity (Lombard et al., 2020; Weaver et al., 2000; Zamuner et al., 2023, 2024), whereas concentrations below these thresholds generally indicate a failure of transfer of passive immunity (FTPI). Additionally, different cut-offs values for some on-farm tools such as Brix refractometry have been described as these values are highly correlated with colostrum and serum IgG concentrations (Kessler

et al., 2021). According to the literature, colostrum Brix values ≥ 22° in cattle (Chigerwe and Hagey, 2014), ≥ 26° in sheep (Hamer et al., 2023) and ≥ 20° in goats (Kessler et al., 2021) are considered indicative of good quality colostrum. Therefore, the acquisition of a correct TPI (i.e., > 10 mg/mL of IgG in calves and > 11.4 mg/mL of IgG in goat kids; Weaver et al., 2000; Zamuner et al., 2023) strictly depends on colostrum quality, timing of colostrum intake and intestinal permeability.

For all the above, low-quality colostrum can result in FTPI, thereby increasing the risk of morbidity and mortality in newborn ruminants. This issue can be strongly linked to inadequate management practices in the last two months of gestation (Caja et al., 2006; Castro et al., 2011b; Weaver et al., 2021). During this period, also known as the dry period, the mammary gland ceases milk production and starts an involution which ultimately ends in colostrum synthesis, also known as colostrogenesis. This dry period is essential not only to guarantee an optimal subsequent lactation but also the health status of the offspring. Therefore, this review aims to address the different factors that influence colostrogenesis during the dry period as well as summarize some novel strategies on colostrogenesis modulation which can impact colostrum quality in dairy goats.

Colostrum synthesis and the role of its bioactive components

Colostrum components are secreted by different mechanisms. The passage of components from blood into the mammary secretion can be either through cells mediated by vesicles, or paracellularly between cells (Lascelles, 1979). In goat colostrum, immunoglobulins represent approximately one third of colostrum total proteins, mainly IgG (90.3%), IgM (6%) and IgA (3.7%) (Rudovsky et al., 2008). There are two subclasses of IgG (i.e., IgG_1 and IgG_2), being IgG_1 the most abundant and representing between 95-98% of the total IgG concentration in colostrum (Micusan and Borduas, 1976). This subclass is present in blood and transferred into colostrum selectively requiring specific receptors such as the neonatal Fc receptor (FcRn; Lu et al., 2007; Sasaki et al., 1976, 1977). However, another source of IgG besides blood circulation appears to be present during colostrogenesis as total IgG in colostrum represents seven times the mass that is present in the individual cow blood (Baumrucker and Bruckmaier, 2014). Therefore, there is still some controversy about the origin of immunoglobulins in colostrum, as the mechanisms that regulate the transfer and local synthesis are still unknown. Other blood components can also reach colostrum through leaky tight junctions between epithelial cells (i.e., leukocytes; Wheeler et al., 2007). Plasma cells and lymphocytes in the mammary gland are able to synthesize and secrete immunoglobulins, cytokines, and enzymes with immunomodulatory activity (Hagiwara et al., 2008). For instance, the enzyme chitotriosidase synthesized by macrophages is capable of hydrolyzing chitin present in the cell wall of fungi and nematodes (Hollak et al., 1994; Renkema et al., 1995) as well as activate other immune cells such as Helper T cells and eosinophils (Wiesner et al., 2015). Interestingly, this enzyme has a greater activity in goat colostrum and blood after parturition compared to the following days postpartum (Argüello et al., 2008; Castro et al., 2011a) having a possible role on protecting both the dam and the newborn

animal around parturition (Argüello et al., 2008). Other locally synthesized components such as oligosaccharides, lactoferrin, active peptides, and hormones can be also secreted into colostrum and seem to have a role in the protection of the newborn animal. Thus, colostrum oligosaccharides can promote growth of beneficial bifidobacteria and improve gut health in calves, enhancing nutrient utilization and ultimately, weight gain (Bunyatratchata et al., 2021). In fact, Marziali et al. (2018) described a decrease of oligosaccharides concentration in goat colostrum from 2.4 to 0.7 mg/mL during the first four days postpartum agreeing with previous studies performed in beef and dairy cows (Fischer-Tlustos et al., 2020). A similar trend is observed for lactoferrin, with significantly higher concentrations found in colostrum (i.e., 387 - 582 µg/ml) compared to mature milk (10 - 28 µg/ml; Hiss et al., 2008; Segura et al., 2024). This iron-binding glycoprotein is capable of binding soluble ferric ion with sufficient affinity to make it unavailable for bacterial growth, acting as a natural antimicrobial agent (Schanbacher et al., 1993). The greater concentrations of these bioactive molecules highlight the crucial role of colostrum in newborns immunity and survival.

Additionally, new studies have focused on milk and colostrum exosomes (Sedykh et al., 2020). They are also known as extracellular vesicles and are considered mediators of cell-to-cell communication as they contain mainly signaling and transcription factors such as RNA and proteins (Doyle and Wang, 2019; Narang et al., 2022). Castro et al. (2024) and Ma et al. (2023) have studied exosomes in goat colostrum finding greater expression of miRNAs involved in cell proliferation, bone homeostasis, and nervous system development in neonates. It seems that the combined effects of these bioactive components may be responsible for the important benefits of colostrum on growth, gut development, and other important physiological functions for the newborn (Fischer-Tlustos et al., 2021). Yet, studies on goat colostrum bioactive components and its effects on health and performance of the offspring are currently scarce.

Onset of colostrogenesis

In cattle, the onset of colostrogenesis occurs approximately three to four weeks before parturition (Brandon et al., 1971,1975). During this period, about 40% of the total mass of IgG present in colostrum is transferred from blood to the secretion (Gross et al. 2014). Similarly, circulating IgG concentrations are reduced 39.7% from the third month of gestation to 15 days before parturition in dairy goats (Castro et al. 2006), which supports the progressive transfer of maternal immune components from blood into colostrum. While numerous studies have investigated the physiological changes occurring during colostrum synthesis (Davis et al., 1979; Fleet et al., 1975; Fleet and Peaker, 1978) none have fully elucidated the specific mechanisms triggering these changes. During the dry period there is an accumulation of nutrients and bioactive components that involves coordinated molecular mechanisms in which the neuroendocrine system plays an important role. Although endocrine pathways regulating colostrogenesis are not completely understood in ruminants, it seems that there is not a specific hormone controlling this process. Instead, colostrogenesis might be tightly regulated by several hormones which act in different stages of colostrum synthesis. It seems that the

main factor contributing to the onset of colostrogenesis is the progressive reduction of circulating progesterone two or three weeks before parturition (Barrington et al., 2001). The decrease of progesterone concentrations occurs simultaneously with the increase of certain galactopoietic hormones (i.e., prolactin and placental lactogen) and estrogens, which promote the transfer of IgG_1 into colostrum by increasing the FcRn receptor activity (Smith et al. 1971; Davis et al. 1979; Barrington et al., 2001). In fact, non-pregnant dry cows treated with a combination of estrogen and progesterone for a week can synthetize a similar fluid in composition to bovine colostrum (Smith et al., 1971), suggesting that these hormones play a crucial role in initiating colostrogenesis, even in the absence of gestation. Increased oxytocin before parturition also induces the impairment of tight junctions between mammary epithelial cells, enhancing the transfer of other immune components into colostrum (Wall et al., 2016). Additionally, the growth hormone has been also proposed to influence this process (Hadsell et al., 1993; Barrington et al., 2001) although the mechanism underlying this regulation is still not well-understood. Certainly, these hormones can regulate colostrogenesis through multiple pathways, not only through the modulation of receptors' activity, but also through the activation of different transcription factors within the mammary epithelial cells (Topper and Freeman, 1980). The complex interaction between hormones, transcription factors, receptors, intracellular intermediates, and extracellular signaling molecules within the mammary gland is likely to trigger the molecular mechanisms responsible for colostrum synthesis (Akers, 2006; Groner, 2002).

Prior to parturition, colostrum will become more liquid and edible due to an increase of prolactin concentrations (Gross et al., 2014; Lacasse et al., 2016) as well as an increased uptake of glucose and a progressive increase of lactose synthesis within the gland that leads to the accumulation of water (Davis et al. 1979; Bigler et al., 2023). Colostrogenesis will cease with the increase of hormones such as prostaglandin F2α (PGF2α) and prolactin during the last days of gestation are likely to determine the end of colostrum synthesis and the onset of milk production (Bigler et al., 2023; Gross et al., 2014). In fact, the induction of parturition using PGF2α analogs can result in reduced colostrum immunoglobulin concentrations in dairy cattle and goats (Field et al., 1989; Castro et al., 2011a). Similarly, the administration of glucocorticoids within 6 to 8 weeks before expected parturition in dairy cows can cease completely the IgG transfer to colostrum (Brandon et al., 1975).

In addition to the endocrine mechanisms influencing colostrogenesis, parity and litter size have been also associated with some changes in colostrum yield and composition in goats. Colostrum yield in multiparous goats is higher than in primiparous goats (Knight and Peaker,1982), which is also supported by Peris et al. (1999) who demonstrated that multiparous goats have greater udder volume and secretory tissue than primiparous goats. This agrees with other dairy species such as cattle and ewes (Adegoke et al., 2016; Fernandez et al., 1995; Walsh et al., 2007). Although no effects of parity and litter size on colostrum yield and composition were reported in *Majorera* dairy goats (Argüello et al. 2006), Romero et al. (2013) found higher protein and lactose percentages in colostrum from

primiparous and single-birth *Murciano-Granadina* goats. In addition, colostrum fat, IgG, INF-γ, and IL-2 concentrations can be higher in twin-birth goats than in single-birth goats (Zhou et al., 2023). These findings suggest that parity and greater litter size can be associated with increased colostrum yield and a possible dilution of components.

Colostrogenesis modulation

Understanding the mechanisms regulating colostrogenesis has opened new paths to develop novel management strategies to enhance colostrum quality. Hereunder are highlighted different dry-off strategies, prepartum diets as well as induced udder inflammation at parturition that can modulate colostrogenesis.

Dry-off management

The dry period, also known as the period between two consecutive lactations, promotes the mammary gland to recover from months of intense milk production. During this period, there is an active reorganization of the mammary gland, preparing the organ for the next lactation. Dairy animals (i.e., cows, ewes and goats) produce milk above the nutritional requirements of the offspring and are not capable of ceasing lactation two months before parturition. The omission of the dry period reduces colostrum IgG concentrations due to a partial inhibition of the mammary gland involution and a continuous milking that prevents the IgG accumulation (Annen et al., 2007; Caja et al., 2006; Safayi et al., 2010). Therefore, it is necessary to modulate the metabolic activity of the gland to reduce milk production and ensure a two-month dry period.

Traditionally, dry-off strategies in dairy cows, sheep and goats have consisted in a progressive reduction of the amount of energy in the diet by reducing cereal grains, a reduction in milking frequency and the application of preventive mastitis treatments (Anniss and Mcdougall, 2002; Bertulat et al., 2015; Petridis and Fthenakis, 2019). However, this last practice tends to be applied occasionally and selectively to prevent unnecessary antimicrobial use and to reduce costs. In addition to the common dry-off strategies, dopamine agonist treatments such as cabergoline have been used in dairy cows (Bach et al., 2015; Boutinaud et al., 2016; Hernández-Castellano et al. 2023), sheep (Caja et al., 2020) and goats (Lacasse et al., 2016) to reduce PRL concentrations in blood and consequently milk yield. Nevertheless, due to the negative effects of these drugs in dairy cows (i.e. hypocalcemia, hypothermia, ataxia, diarrhea and in some cases death) this product was banned by the European Medicines Agency in 2019. In dairy sheep and goat, the use of melatonin implants has become a common practice to stimulate estrus and ovulation (Elhadi et al., 2022). However, melatonin also promotes an efficient mammary gland reorganization during the dry period and increases milk yield in the subsequent lactation in both species (Avilés et al., 2019; Misztal et al., 2018) although the effect of these implants on colostrum quality remains unknown. Therefore, future studies should focus on developing novel and efficient dry-off strategies to not only promote a healthy lactation but also to guarantee a successful colostrum synthesis.

Nutrition management

The development of the mammary gland begins before parturition, a period in which the uptake of blood-derived molecules will progressively increase and accumulate in the udder. Consequently, the uptake of nutrients during the dry period can impact colostrum yield and composition (Hare et al. 2023). Indeed, a nutrient restriction during gestation causes reduced colostrum yield in dairy cows and sheep without affecting IgG concentration (Logan, 1977; Banchero et al., 2006; Zarrin et al., 2021). Although the effects of feed restriction on goat colostrum have not been addressed yet, a similar yield reduction is expected. In contrast, exceeding energy requirements in dairy cows during colostrogenesis does not affect colostrum yield (Daneshvar et al., 2020; Fischer-Tlustos et al., 2021) nor IgG concentrations (Dunn et al., 2017; Springer et al., 2008), although Mann et al. (2016) described reduced IgG concentrations in colostrum from cows fed above the metabolizable energy requirements prepartum. Similarly, feeding dairy ewes and goats above the energy requirements during the last month of gestation does not affect either colostrum yield or immunoglobulin concentrations (Celi et al., 2008; Gallo et al. 2020). However, Ramírez-Vera et al. (2012) found greater colostrum yield and lactose percentage in grazing goats that were supplemented with corn starch 12 days before expected parturition.

Although limited data is available in goats, dietary supplementation, or inclusion of different sources of protein and fat in late gestation does not seem to influence colostrum yield and composition. According to Shabrandi et al. (2019), a prepartum metabolizable energy (ME) and metabolizable protein (MP) supplementation (i.e., 10% of NRC recommendations) can cause greater mammary gland development in dairy goats, although colostrum yield being not affected. Similar results were observed in dairy ewes supplemented with 116.5 g crude protein (CP) and 84.6 g MP/kg dry matter (DM) compared to the control group that received 99.4 g of CP and 70.5 g MP/kg DM (Mousavi et al. 2016). However, results across studies remain inconsistent as some authors have found higher protein concentrations in ewe colostrum after protein supplementation during late gestation (Amanlou et al., 2011). Differences among these studies might be caused by the source and type of protein (i.e., rumen degradable *vs*. undegradable protein) and length of supplementation (i.e., 3 *vs*. 6 weeks before expected parturition date). Prepartum fat supplementation has been also tested in ruminants. In dairy cows, prepartum fat supplementation increases colostrum IgG and fatty acids concentrations but does not affect colostrum yield (Ricks et al., 2020). Unlike in cattle, the supplementation with conjugated linoleic acid from the third month of gestation does not increase colostrum IgG concentration in dairy goats (Castro et al., 2006). Similarly, Moreno-Indias et al. (2014) found that supplementing pregnant dairy goats with 5 g/day of *Chlorella pyrenoidosa as a* source of unsaturated fatty acids and essential aminoacids (Chen et al., 2022; Kouřimská et al., 2014) does not have any effect on yield, fatty acids profile and immune components in colostrum. However, Cattaneo et al. (2006) described that 1.1% fish oil supplementation during the last three weeks before parturition increases long-chain n-3 polyunsaturated fatty acids, mainly eicosapentaenoic and docosahexaenoic acid, in dairy goat colostrum. In ewes, fish oil supplementation during the dry period has

a negative impact on colostrum yield as well as in fat, protein, and IgG concentrations (Annett et al., 2009). The differences observed among studies might be associated with factors such as nutrient source, timing and length of supplementation, breed and management system that can directly influence the degree of response to the dietary supplementation. Although increasing certain macro- and micronutrients during the last weeks of gestation seems to positively impact colostrum yield and composition in dairy goats, future studies need to characterize the effects of different dietary strategies in both colostrum chemical composition and less abundant bioactive compounds.

Colostrogenesis and intramammary health

The epithelial cells and connective tissue forming the alveoli in the mammary gland create a structure known as blood-milk barrier (BMB) which regulates the transfer of components between blood and milk. Linzell and Peaker (1971) carried out the first studies on mammary gland permeability in lactating goats, describing that the differences between colostrum and milk composition could be caused by structural changes in the tight junctions between epithelial cells during late gestation. It seems that the mechanisms underlying changes in the BMB permeability are complex and could be associated with hormonal changes that induce modifications in the mammary tight junctions. During inflammation, the BMB becomes permeable allowing the passage of immune cells and factors such as lymphocytes, neutrophils, and antibodies from blood to the lumen of the alveoli and consequently into milk (Burton and Erskine, 2003; Wellnitz and Bruckmaier, 2021.). The recruited immune cells secrete IgG_1, IgG_2, IgM and cytokines enhancing pathogen phagocytosis, which in turn increases the somatic cell count (SCC) in milk (Wall et al., 2018; Wellnitz et al., 2015). No changes have been detected in colostrum immunoglobulin concentrations from either primiparous or multiparous Holstein cows with natural occurring mastitis (Maunsell et al.,1998; Enger et al., 2021). However, Bruckmaier and Wellnitz (2017) observed blood-derived constituents in milk (i.e., serum albumin, LDH and IgG) after inducing an experimental mastitis in dairy cows. Cell-wall components such as lipopolysaccharides (LPS) from gram-negative bacteria (*Escherichia coli*) as well as lipoteichoic acid (LTA) or peptidoglycans (PGN) from gram-positive bacteria (*Staphylococcus aureus*) have been widely used to mimic sterile mastitis in experimental conditions (Kusebauch et al., 2018; Wellnitz et al., 2013), observing different immune components in milk from cows treated with LPS compared to those treated with either LTA or PGN. Although the induction of udder inflammation has been mainly used to assess the mammary immune response to determine better approaches to treat mastitis in dairy cows, some studies have also assessed its impact on milk and colostrum composition. Danielsen et al. (2010) described changes in the milk proteome profile of dairy cows in response to an intramammary LPS challenge (i.e., 200 mg *Escherichia coli* serotype O111:B4) reporting an upregulation of acute phase proteins, immunoglobulins and complement factors as well as an increase of α-, β-, and k-caseins after 7 h of the LPS challenge. Similarly, higher protein and lower lactose percentages have been reported in milk from *Murciano-Granadina* dairy goats challenged with 10 µg of intramammary LPS (*Escherichia coli* serotype O55:B5; Salama et al. 2020). Aiming to assess these effects on colostrum

composition, González-Cabrera et al. (2024a) showed that the intramammary infusion of 2 mL of saline containing 50 µg of LPS (*Escherichia coli* serotype O55:B5) in each half udder at parturition caused increased IgG and IgM concentrations in colostrum without any sign of local inflammation or discomfort. In agreement with these findings, Alcindo et al. (2023) also reported higher colostrum IgG concentrations in response to a natural infection in dairy goats. These strategies are of special interest in goats producing low-quality colostrum, as it has been demonstrated that the absorption capacity of macromolecules (i.e., immunoglobulins) in the newborn animal can be already saturated when providing high-quality colostrum (González-Cabrera et al., 2024b; Saldana et al., 2019). In addition, feeding newborn goat kids with colostrum derived from LPS-treated goats is safe as no signs of disease has been reported (González-Cabrera et al., 2024b). In support of these findings, Samarasinghe et al. (2020) showed that the administration of LPS (i.e.,12 µg/kg of BW) in milk did not induce any acute inflammatory response in one-month old Holstein calves, suggesting that oral intake of LPS has no detrimental effects on the health status of the animals. However, it should be considered that these molecules (i.e., LPS, LTA or PGN) could be absorbed if the intestinal permeability is impaired (i.e., leaky gut), causing a systemic immune response that may compromise animal health. Besides this, modulation of the BMB permeability through an induced immune response might still have remarkable applications. For instance, increased permeability combined with the vaccination against certain pathogens could enhance the transfer of specific antibodies from blood to colostrum and milk, promoting a better immunization of the offspring. Therefore, and despite mastitis has evident detrimental effects on performance and health in dairy animals, inducing a moderate and local immune response within the udder might be used to positively modulate colostrum quality.

Conclusions

In ruminants, colostrogenesis is a well-preserved mechanism that seems to be essentially regulated by the neuroendocrine system. However, multiple factors such as dry-off management practices, the inclusion of different nutrients on prepartum diets, and udder inflammation can also impact colostrogenesis and consequently, be used strategically to enhance colostrum quality. However, there is still the need to deeply assess the effects of macro and micronutrients supplementation in late gestation to develop better nutritional strategies to modulate and promote colostrum yield and composition in dairy ruminants. Inducing a mammary gland immune response seems to trigger helpful modifications on the blood-milk barrier enhancing colostrum immune composition. Future studies should focus on developing optimal management and nutritional strategies during late gestation to enhance colostrum quality and consequently, offspring health and performance.

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Table 1. Goat kid mortality rates before weaning

Region/Country	Mortality rate, %	Breed	Management system	Reference
Africa				
Ethiopia	31 – 42	Arsi-Bale & Borana	Extensive	(Hailu et al., 2006)
Ghana	10	West African Dwarf	Intensive	(Turkson et al., 2004)
Morocco	16	Beni Arouss & Northen Morocco	Extensive	(Bahri et al., 2021)
South Africa	8.6 - 16.5	Angora	Extensive	(Snyman, 2010)
America				
Canada	20 – 30	Saanen & Alpine	Intensive	(Rätsep, 2020)
U.S.A.	10 -14	n/s	n/s	(USDA, 2012)
Asia				
India	8.92 - 57.7	Sirohi & LB	Semi-intensive	(Chauhan et al., 2019) (Perumal et al., 2019)
Jordan	13	Crossbred Shami	Extensive	(Aldomy et al., 2009)
Sri Lanka	23.7 - 32.2	South Indian & LB	Extensive	(Ranatunga, 1971)
Europe				
Germany	16.1 - 24.1	Alpine & Saanen	n/s	(Balasopoulou et al., 2022)
Netherlands	4.3	n/s	Intensive	(Dijkstra et al., 2023)
Spain	21	MG & MG × Boer	Intensive	(Fernández et al., 2021)
Oceania				
Australia	20	Boer & Kalahari Red	n/s	(Robertson et al., 2020)
New Zealand	5.9 - 20.5	n/s	Intensive	(Todd et al., 2019)

Abbreviation: n/s = not specified; LB = local breed; MG = Murciano-Granadina

Capítulo 4

Chapter 4

Efecto del aporte de dietas ricas en almidón durante el último mes de gestación en la calidad del calostro, así como en el estado inmune y metabólico de cabras y cabritos

Effects of feeding dairy goats with a high-starch diet prepartum on colostrum quality, and dam and goat kid metabolism and immune status

Manuscript ready for submission in Journal of Dairy Science

RESUMEN

La alimentación durante la lactación y la gestación puede influir en la producción y composición de la leche, así como en el desarrollo de las crías. El presente estudio tiene como objetivo estudiar el efecto del aporte de una dieta con alto contenido de almidón a cabras lecheras durante el último mes de gestación, sobre la producción y composición del calostro, el estado metabólico e inmune de las cabras, así como el metabolismo, el estado inmune y el crecimiento de los cabritos. Treinta cabras multíparas y gestantes de raza Majorera fueron asignadas aleatoriamente a una de las dos dietas experimentales (control *vs*. HS) desde la semana -4 relativa a la fecha estimada de parto hasta el parto. Las cabras fueron alimentadas con una dieta control (n = 15; 100% MS de los requerimientos de almidón) o con una dieta HS (n = 15; 134% MS de los requerimientos de almidón) de acuerdo con las recomendaciones para cabras en último mes de gestación publicadas por *L´Institut National de la Recherche Agronomique* (INRA, 2018). Se tomaron muestras de sangre en las semanas -4, -3, -2 y -1 relativas al parto, inmediatamente después del parto y en los días 1, 2, 3, 5, 10, 15, 30 postparto. Durante este período se evaluó la producción y la composición química del calostro y la leche, el recuento de células somáticas (SCC), la concentración de IgG en calostro, leche y plasma, los metabolitos séricos en las madres, así como el consumo, el peso y los metabolitos séricos en los cabritos. A pesar de no observarse diferencias en la producción y la composición química del calostro, las cabras alimentadas con la dieta con alto contenido en almidón mostraron concentraciones más elevadas de IgG en el calostro en comparación con el grupo control (85,4 ± 8,39 y 60,5 ± 8,3 mg/ml, respectivamente). La dieta no influyó en la leche de transición ni en la leche madura. Sin embargo, la concentración sérica de β-hidroxibutirato en el grupo HS aumentó progresivamente hasta el parto, mientras que el grupo control mostró un aumento brusco desde la semana -1 hasta el parto (0,24 ± 0,02 y 0,29 ± 0,02 mmol/l en el parto, respectivamente). Las concentraciones de calcio, proteína total, lactato deshidrogenasa, urea y albúmina fueron más bajas en el grupo HS que en el grupo control durante el período preparto. La dieta con alto contenido en almidón no influyó en los metabolitos séricos en el período postparto, excepto en la enzima lactato deshidrogenasa, que mostró concentraciones más bajas en el grupo HS. En los cabritos,

el consumo, el peso y las concentraciones plasmáticas de IgG no se vieron influenciadas por la dieta de las madres, excepto en la concentración de proteína total sérica que se vio aumentada en los cabritos del grupo HS. Los resultados indican que alimentar a las cabras gestantes con una dieta con alto contenido en almidón durante el último mes de gestación promueve una transición progresiva entre el final de la gestación y el comienzo de la lactación al generar una movilización de reservas grasas menos marcada, lo que reduce el impacto del balance energético negativo antes del parto. Además, si bien la producción o la composición química del calostro no se vieron influenciadas, la alimentación con alto contenido en almidón aumentó la concentración de IgG en el calostro, sin inducir cambios en el crecimiento, el metabolismo y la transferencia de inmunidad pasiva en los cabritos.

Interpretative summary. Effects of feeding dairy goats with a high-starch diet prepartum on colostrum quality, and dam and goat kid metabolism and immune status. By González-Cabrera et al.

This study aimed to investigate the effects of feeding a high-starch diet during the last month of gestation on colostrum quality and dam and goat kid metabolism and performance. Results indicate that exceeding dietary starch during colostrogenesis does not influence colostrum yield or gross chemical composition but increases IgG concentration. In addition, it promotes a smoother transition from late pregnancy to early lactation, reducing the extent of fat mobilization in the dams. Despite the greater colostrum IgG concentration, feeding a maternal high-starch diet prepartum does not enhance the transfer of passive immunity and growth of the offspring.

Running head: PREPARTUM HIGH-STARCH DIET ON GOAT COLOSTRUM

Effects of feeding dairy goats with a high-starch diet prepartum on colostrum quality, and dam and goat kid metabolism and immune status.

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ABSTRACT

This study hypothesizes that feeding a high-starch (HS) diet during the last month of gestation enhances colostrum yield and composition, the dam metabolic and immune status as well as the goat kid metabolism, immune status and performance. Thirty multiparous pregnant *Majorera* dairy goats were randomly assigned to a prepartum dietary treatment (control *vs*. HS) on wk -4 relative to expected parturition. Goats were fed either a control (n = 15; 100% DM of starch requirements) or HS (n = 15; 134% DM of starch requirements) diet during the last month of gestation according to INRA (2018) guidelines. Blood samples were collected on wk -4, -3, -2, and -1 relative to expected parturition, immediately at parturition (d0) and on d 1, 2, 3, 5, 10, 15, 30 postpartum. Yield was recorded and chemical composition, SCC and IgG concentration determined. In addition, dam and goat kid serum metabolites and plasma IgG concentration were analysed. Data were analysed using the MIXED and ANOVA procedure of SAS (SAS 9.4). The model included the prepartum diet (D), time (T), and the interaction between both as fixed effects. The statistical significance was set as $P \leq 0.05$. No differences were obtained for colostrum yield and chemical composition, whereas higher colostrum IgG concentration was observed in the HS group compared to the control group (i.e., 85.4 ± 8.39 and 60.5 ± 8.30 mg/mL, respectively). Transition and whole milk were not affected by the prepartum high-starch diet. However, serum BHB concentration in the HS group increased progressively until parturition, whereas the control group showed a sharp increase from wk -1 to parturition (i.e., 0.24 ± 0.02 and 0.29 ± 0.02 mmol/L at parturition, respectively). Calcium, total protein, lactate dehydrogenase, urea and albumin concentrations were lower in the HS group compared to the control group during the prepartum period. The high-starch diet prepartum did not influence serum metabolites in the postpartum period except for lactate dehydrogenase, showing lower concentration in the HS group. In goat kids, BW, milk intake

and plasma IgG concentrations were not affected by the high-starch diet offered to the dams prepartum except for an increased serum total protein concentration observed in goat kids from the HS group. The present results indicate that a high-starch diet during the last month of gestation does not affect either colostrum yield or composition but increases colostrum IgG concentration. In addition, it also promotes a smoother transition from late pregnancy to early lactation in dairy goats, without affecting growth, metabolism, and transfer of passive immunity in goat kids.

***Key words*:** energy, late gestation, colostrogenesis, performance, physiology

Abbreviations

BHB = β-hydroxybutyrate
FFA = Free fatty acids
HS = High-starch
IgG = Immunoglobulin G
LDH = Lactate dehydrogenase
MI = Individual milk intake
NEB = Negative energy balance
RT = Rectal temperature
T = Time
TP = Total protein

INTRODUCTION

Studies on dairy and beef cattle reported that prepartum nutrition impacts lactation and offspring performance (Keady et al., 2005; Chung et al., 2008; Moriel et al., 2021; Zang et al., 2022). Similar studies performed on sheep and goats suggest that prepartum nutritional management influences milk yield and shapes offspring health and performance (Sahlu et al., 1995; Shabrandi et al., 2019; Villar et al., 2023). During the last two months of gestation, dairy ruminants experience important metabolic adaptations caused by the increased energy demand

for foetal growth as well as for the mammary gland development to face a new lactation (Eley et al., 1978; Castagnino et al., 2015). During this reorganization, the mammary gland synthesizes colostrum, which starts 3-4 weeks before kidding. After parturition, dairy animals must also increase energy intake to face the high energy requirements for milk synthesis. Starch is one of the main nutrients in ruminant diets often used in replacement of forage to increase energy supply. This carbohydrate is present in cereal grains such as maize or wheat and is rapidly fermented by the rumen microbiota into propionate, which is absorbed into the bloodstream to be used as a glucose precursor. The benefits of concentrate supplementation during lactation are well-known in dairy cows, sheep and goats (Gómez-Cortés et al., 2018; Lunesu et al., 2021a; 2021b; Haisan et al., 2021).

High-starch diets are used after parturition to reduce the negative energy balance (**NEB**) during early lactation (Reynolds et al., 2001; McCarthy et al., 2015). However, feeding high-starch diets during the last months of gestation can enhance gut adaptation to highly fermentable diets and reduce fat mobilization during lactation in ruminants such as dairy cows (Janovick et al., 2011), sheep (Banchero et al., 2004b) and goats (Celi et al., 2008). In addition, Banchero et al. (2009) observed reduced neonatal mortality rates in lambs born from sheep fed *Lotus uliginosus* pasture and whole maize during the last two weeks of gestation. However, this practice often increases the risk of rumen acidosis which can lead to reduced feed intake and consequently, reduced milk production having a negative impact on dam health and performance (Zebeli and Metzler-Zebeli, 2012).

Although the effects of nutrition during lactation are well-documented, there is limited knowledge about the effects of feeding high-starch diets prepartum on colostrum yield and composition in dairy goats raised under intensive management systems as well as their influence on the offspring. Therefore, this study hypothesizes that feeding a high-starch diet during the last month of gestation increases colostrum yield and enhances colostrum

102 composition, and the metabolic and immune status of both dairy goats and goat kids. Based on
103 this, the present study aimed to investigate the effect of feeding a high-starch diet prepartum
104 on colostrum yield and composition and on the metabolic and immune status of the dams and
105 their goat kids.

106 **MATERIAL AND METHODS**

107 All experimental procedures were approved by the Ethical Committee for Animal
108 Experimentation of the Universidad de Las Palmas de Gran Canaria (OEBA-ULPGC 03/2023;
109 OEBA-ULPGC 04/2023).

110 ***Experimental Design***

111 Thirty multiparous *Majorera* dairy goats within the second and fourth lactation housed in a
112 free-stall barn were randomly assigned to a prepartum dietary treatment at wk -4 relative to
113 expected parturition. Groups were balanced by BW (i.e., 64.6 ± 1.14 kg) and the animals were
114 fed either a control (n = 15 [**CON**]; 100% starch requirements, DM basis) or a high-starch (n
115 = 15 [**HS**]; 134% starch requirements, DM basis) diet during the last month of gestation. All
116 diets were isoproteic and formulated following the guidelines provided by the *L'Institut*
117 *National de la Recherche Agronomique* (INRA; Sauvant et al., 2018) to either meet or exceed
118 the starch requirements for dry goats in the last month of gestation (Table 1). Each animal was
119 individually fed concentrate divided in two meals (50% each meal, at 0730 am and 1700 pm)
120 while forage was provided daily in the free stall. Additionally, all the animals had access to
121 fresh water and mineral blocks (i.e., Na, 36.0 g/kg; Ca, 1.00 g/kg; Mg, 0.6 g/kg; $MnSO_4$, 312
122 mg/kg $FeSO_4$, 200 mg/kg; Na_2SeO_3, 33 mg/kg; Ca (IO_3), 24 mg/kg; $(CH_3COO)_2Co*_4H_2O$, 8
123 mg/kg). After parturition, both groups received a diet to meet the requirements for dairy goats
124 in the first month of lactation (Table 1). After parturition, goats were milked once a day at 0730
125 h in a double 12-stall parallel milking parlor (Alfa Laval Iberia SA, Madrid, Spain) equipped

with recording jars (3.5 L ± 5%) using the procedure described by Torres et al. (2013). Single and twin-born goat kids with a birth BW > 2.5 kg (n = 43) were immediately separated from the dam after birth and allocated to either the HS group (n = 25) or the CON group (n = 18) depending on the experimental group of the dam. Goat kids were bottle-fed with their dam's colostrum (10% of the birth BW) divided in two meals within the first 12 h of life (i.e., at 2 and 12 h relative to birth). After that, animals were fed twice daily with whole goat milk using teat feeding buckets. The health status of both dairy goats and goat kids was monitored daily.

Data and sample collection

The experiment started at wk -4 relative to expected parturition and finished on wk 4 postpartum. Throughout the study, the amount of concentrate offered and refused (as-fed basis) was recorded daily. Dams BW was recorded weekly during the entire experimental period. Blood samples from the dams were collected from the jugular vein using 10 mL syringes (Injekt Braun, Braun, Germany) and 20G needles (Sterican Braun, Braun, Germany) on wk -4, -3, -2, -1 relative to expected parturition, immediately at parturition (d 0) and then on d 1, 2, 3, 5, 10, 15 and 30 postpartum. In the goat kids, blood samples were always collected before feeding and following the same sampling scheme as the dams postpartum. Blood was immediately transferred to EDTA-K2 tubes (BD Vacutainer, UK) for plasma collection, and serum tubes (SEROTUB, DeltalabTM, Spain) to obtain blood serum. Plasma tubes were placed on ice immediately after collection and centrifuged at 2190 × g for 10 min at 4°C (Hettich Zentrifugen, Universal 32 R, Tuttlingen, Germany). Serum tubes were stored at room temperature for 2 h and then centrifuged at 2190 × g for 10 min at 4°C. Both plasma and serum were aliquoted in 1.5 mL Eppendorf tubes and stored at -20°C until further analysis. Colostrum was collected at parturition (d 0) followed by transition milk (i.e., d 1, 2 and 3 relative to parturition), and whole milk (i.e., d 5, 10, 15 and 30 relative to parturition) collection. Animals were milked completely in the milking parlour where colostrum and milk yields were recorded.

Individual milk intake (**MI**), RT and BW of goat kids were recorded at birth and on d 5, 10, 15 and 30 of life.

Sample analysis

Blood, colostrum and milk samples were analysed for immunoglobulin G (**IgG**) concentration using a commercial ELISA kit (Bethyl Laboratories, Montgomery, TX, USA). The intra-assay and inter-assay coefficients of variation were 4.41% and 4.86%, respectively. Concentrations of β-hydroxybutyrate (**BHB**; 137019910930, DiaSys Diagnostics, Holzheim, Germany), calcium (GN12125, RAL laboratories, Barcelona, Spain), free fatty acids (**FFA**; 157819910935, DiaSys Diagnostics, Holzheim, Germany), glucose (GN45126, RAL laboratories, Barcelona, Spain), lactate dehydrogenase (**LDH**; GN42125, RAL laboratories, Barcelona, Spain), total proteins (**TP**; GN46125, RAL laboratories, Barcelona, Spain), albumin (GN86125, RAL laboratories, Barcelona, Spain) and urea (GN70125, RAL laboratories, Barcelona, Spain) were measured in blood serum using an automatic spectrophotometer (METROLAB 2300GL, RAL laboratories, Barcelona, Spain). The intra-assay coefficients of variation were 0.56, 2.10, 1.10, 1.92, 1.07, 0.90, 0.50 and 2.79%, respectively. The inter-assay coefficients of variation were 2.15, 3.09, 2.16, 3.10, 1.15, 1.43, 0.80 and 2.65%, respectively.

Colostrum and milk chemical composition (i.e., fat, protein, lactose, and total solids) were determined by infrared spectroscopy using a MilkoScanTM Mars (FOSS IBERIA, Spain). Colostrum samples were diluted 1:4 (v/v) using deionized water based on the procedure described by Spina et al. (2021) and Soufleri et al. (2023). Somatic cells count (**SCC**) in colostrum and milk was determined using a DeLaval cell counter (DeLaval, Tumba, Sweden). Samples with SCC greater than 3000 10^3 cells/mL were diluted 1:5 (v/v) with saline solution as described by Kawai et al. (2013). In addition, a digital refractometer (PAL-1, ATAGO CO., LTD., Tokio, Japan) was used to determined Brix° in colostrum and milk samples.

Statistical Analysis

The POWER procedure of SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) determined 13 animals per group as the minimum number of animals required to set a significant effect on colostrum IgG concentration (differences between groups > 6.8 mg of IgG per mL) based on previous literature (41.1 mg/mL with a SD of 5.65 mg/mL; Hernández-Castellano et al., 2016). The significance level was set as 5% and the power as 80%.

The residual distributions of the data were assessed using the UNIVARIATE procedure of SAS (SAS 9.4). Data which did not follow normal distributions were log-transformed (log10) to get a normal distribution of residues and homogeneity. Results are presented as Least Square Means (LSM) ± SEM. The Bonferroni test was used to determine significant differences ($P \leq 0.05$). Prepartum and postpartum data were analysed separately using the MIXED procedure of SAS (SAS 9.4). Data on wk -4 were set as the baseline for the prepartum data (wk -3, -2, -1 and d 0) and d 0 data were set as the baseline for the postpartum data (d 1, 2, 3, 5, 10, 15, and 30). Therefore, the model included diet (HS *vs*. CON), time (wk -3 to d 0 for prepartum data and d 1 to d 30 for postpartum data) and the interaction between both (Diet × Time) as fixed effects. The animal (i.e., goat or goat kid) was considered as an individual subject, time as a repeated measure and litter size as a random effect. Colostrum data were analysed using the ANOVA procedure of SAS (SAS 9.4) and the model included the diet (HS *vs*. CON) as a fixed effect and the animal (i.e., goat) as an individual subject.

RESULTS

Throughout the study, three dams were removed due to health problems, including one abortion. Therefore, the final experimental size for each group was HS n = 13 and CON n = 14. Gestation length and litter size were 150 ± 1.3 days and 1.68 ± 0.10 kids, respectively. No

differences in birth BW were observed between groups (3.0 ± 0.24 and 3.2 ± 0.24 kg in HS and CON goat kids respectively; P = 0.503).

Blood metabolites in dairy goats prepartum

Plasma IgG concentration was not affected either by the prepartum diet (Table 2; P = 0.533) or time (P = 0.723). A two-way interaction was observed for serum BHB (Table 2; Figure 1A; P = 0.006). The BHB concentration in the HS group increased constantly from wk -3 to parturition (0.20 ± 0.02 and 0.24 ± 0.02 mmol/L, respectively) whereas BHB concentration decreased from wk -3 to wk -2 (0.22 ± 0.02 and 0.19 ± 0.02 mmol/L, respectively), and then increased until parturition (0.29 ± 0.02 mmol/L) in the CON group. Calcium and TP concentrations were affected by the prepartum diet (Table 2; P ≥ 0.019). The HS group showed lower calcium and TP concentrations (7.1 ± 0.16 mg/dL and 6.1 ± 0.16 g/dL, respectively) than the CON group (7.6 ± 0.16 mg/dL and 6.7 ± 0.16 g/dL, respectively) during the entire prepartum period (wk -3 to parturition). In contrast, serum FFA concentration was not affected by the prepartum diet (Table 2; P = 0.793) but was affected by time (P < 0.001) increasing from wk -3 to parturition (0.25 ± 0.04 and 0.52 ± 0.04 mmol/L, respectively). Glucose concentration was not affected by either the prepartum diet (Table 2; P = 0.135) or time (P = 0.938). However, LDH, albumin and urea concentrations were affected by both the prepartum diet (Table 2; P ≤ 0.039) and time (P ≤ 0.007). Serum LDH, albumin and urea concentrations were lower in the HS group (362.7 ± 23.81 U/L, 3.0 ± 0.07 g/dL and 22.2 ± 2.25 mg/dL, respectively) compared to the CON group (441.5 ± 23.81 U/L, 3.3 ± 0.07 g/dL and 32.0 ± 2.25 mg/dL, respectively). In addition, LDH, albumin and urea concentrations in both groups increased progressively from wk -3 (367.4 ± 26.0 U/L, 3.1 ± 0.06 g/dL and 24.7 ± 2.20 mg/dL, respectively) to parturition (454.1 ± 26.0 U/L, 3.2 ± 0.06 g/dL and 30.6 ± 2.20 mg/dL, respectively).

Blood metabolites in dairy goats postpartum

Plasma IgG concentration was not affected by the prepartum diet (Table 3; P = 0.414) but was affected by time (P < 0.001), increasing constantly from d 1 to d 30 (18.2 ± 0.78 and 21.1 ± 0.78 mg/mL, respectively). Similarly, BHB, calcium, TP and albumin concentrations were not affected by the prepartum diet (Table 3; P ≥ 0.093) but were affected by time (P ≤ 0.019). Serum BHB concentrations increased from d 1 to d 2 (0.5 ± 0.04 and 0.6 ± 0.04 mmol/L, respectively), decreasing on d 3 (0.5 ± 0.04 mmol/L) and then increased progressively until d 30 (0.6 ± 0.04 mmol/L). Calcium concentration increased constantly from d 1 to d 30 (7.2 ± 0.30 and 7.9 ± 0.30 mg/dL, respectively), as well as TP (6.5 ± 0.16 and 7.6 ± 0.16 g/dL, respectively) and albumin concentrations (3.1 ± 0.10 and 3.4 ± 0.10 g/dL, respectively). In contrast, LDH concentration was not affected by time (Table 3; P = 0.456), but was affected by the prepartum diet (Table 3; P = 0.019) being lower in the HS group than in the CON group (473.0 ± 22.23 and 552.8 ± 22.23 U/L, respectively). An interaction between the prepartum diet and time (Table 3; P = 0.028) was observed for urea concentration. In the HS group, urea concentration increased from d 1 to d 2 (33.1 ± 2.29 and 37.9 ± 2.25 mg/dL, respectively), decreasing until d 5 (35.1 ± 2.33 mg/dL) and increasing again until d 30 (41.3 ± 2.56 mg/dL), whereas the CON group decreased from d 1 to d 3 (39.3 ± 2.21 and 35.8 ± 2.18 mg/dL, respectively) and then increased progressively until d 30 (43.7 ± 2.22 mg/dL). Glucose and FFA concentrations were not affected by either the prepartum diet (Table 3; P ≥ 0.304) or time (P ≥ 0.154).

Colostrum and milk variables in dairy goats

Colostrum yield, chemical composition, SCC and Brix degrees were not affected by the high-starch diet prepartum (Table 4; P ≥ 0.150). However, colostrum IgG concentration was affected by the high-starch diet prepartum (Table 4; P = 0.047), being higher in the HS group than in the CON group (85.4 ± 8.39 and 60.5 ± 8.39 mg/mL, respectively).

Transition milk yield, chemical composition, SCC, Brix and IgG concentration were not affected by the high-starch diet prepartum (Table 5; $P \geq 0.085$). However, TM yield, lactose, protein, and total solids percentages, Brix degrees and IgG concentration were affected by time (Table 5; $P \leq 0.001$). Transition milk yield increased from d 1 to d 3 (1.4 ± 0.11 and 2.0 ± 0.11 kg/d, respectively) as well as lactose percentage (3.6 ± 0.10 and 4.2 ± 0.10 %, respectively). In contrast, protein and total solids percentages decreased from d 1 (8.2 ± 0.29 and 20.0 ± 0.51 %, respectively) to d 3 (5.9 ± 0.27 and 17.3 ± 0.46 %, respectively). Similarly, Brix degrees and IgG concentration decreased from d 1 (16.7 ± 0.63° and 28.3 ± 2.79 mg/mL, respectively) to d 3 (12.3 ± 0.58° and 7.01 ± 2.64 mg/mL, respectively).

Whole milk yield, chemical composition, SCC, Brix degrees and IgG concentration were not affected by the high-starch diet prepartum (Table 6; $P \geq 0.115$). Despite lactose was not affected by time (Table 6; $P = 0.429$), protein, total solids and fat percentages decreased over time (Table 6; $P < 0.001$). Protein percentage decreased constantly from d 5 to d 30 (4.6 ± 0.08 and 3.7 ± 0.08 %, respectively) as well as total solids (15.4 ± 0.16 and 13.4 ± 0.16 %, respectively). However, fat percentage decreased from d 5 to d 15 (5.5 ± 0.17 and 3.9 ± 0.17 %, respectively) and then increased until d 30 (4.2 ± 0.17 %). Similarly, Brix degrees and IgG concentration were affected by time (Table 6; $P < 0.001$) decreasing from d 5 (12.0 ± 0.16° and 2.8 ± 0.19 mg/mL, respectively) to d 30 (10.8 ± 0.16° and 1.4 ± 0.19 mg/mL, respectively).

Blood metabolites and performance in goat kids

Body weight and MI were not affected by the maternal high-starch diet prepartum (Table 7; $P \geq 0.338$). However, both MI and BW increased from d 5 (862.0 ± 50.03 mL and 3.4 ± 0.18 kg, respectively) to d 30 (1418 ± 50.03 mL and 7.0 ± 0.18 kg, respectively; $P < 0.001$). Rectal temperature was not affected by the maternal high-starch diet prepartum (Table 7; $P = 0.150$)

but was affected by time ($P < 0.001$), increasing from birth to d 10 (38.5 ± 0.08 and 39.4 ± 0.08 °C, respectively) and decreasing until d 30 (39.2 ± 0.08 °C).

A two-way interaction between diet and time was observed for serum TP concentration ($P = 0.011$). Total protein concentration in goat kids from the HS group increased from d 0 to d 1 (4.7 ± 0.15 and 7.1 ± 0.15 g/dL, respectively) decreasing progressively until d 15 (5.8 ± 0.15 g/dL) and increasing again until d 30 (6.1 ± 0.15 g/dL). The CON group showed increased TP concentrations from d 0 to d 2 (4.7 ± 0.22 and 6.5 ± 0.22 g/dL, respectively), decreasing progressively until d 10 (5.8 ± 0.22 g/dL) and increasing again until d 30 (6.1 ± 0.22 g/dL). The rest of the serum variables (i.e., Calcium, glucose, LDH, albumin and urea) were not affected by the maternal high-starch diet (Table 7; $P \geq 0.117$) but were affected by time (Table 7; $P < 0.001$). Albumin concentration decreased from d 0 to d 3 (2.9 ± 0.05 and 2.5 ± 0.05 g/dL, respectively) and then increased progressively until d 30 (3.5 ± 0.05 g/dL). Similarly, calcium concentration decreased from d 0 to d 2 (11.1 ± 0.18 and 10.1 ± 0.18 mg/dL, respectively) increasing until d 5 (10.5 ± 0.18 mg/dL) and then decreased again until d 30 (9.8 ± 0.18 mg/dL). Lactate dehydrogenase concentration increased from d 0 to d 1 (776.0 ± 38.73 and 849.2 ± 35.41 U/L, respectively), decreased on d 3 (558.3 ± 34.7 U/L) and then increased progressively until d 30 (969.4 ± 35.61 U/L). Similarly, urea concentration increased from d 0 to d 1 (43.1 ± 1.76 and 62.7 ± 1.65 mg/dL, respectively), decreasing until d 30 (40.1 ± 1.62 mg/dL). In contrast, glucose concentration increased from d 0 to d 30 (12.4 ± 4.56 and 105.3 ± 4.30 mg/dL, respectively).

Similarly, plasma IgG concentration was not affected by the maternal high-starch diet (Table 7; $P = 0.796$) but was affected by time ($P < 0.001$). Plasma IgG concentration increased from d 0 to d 2 (0.7 ± 0.82 and 15.7 ± 0.70 mg/mL) and then decreased progressively until d 30 (6.2 ± 0.70 mg/mL).

DISCUSSION

Dietary modifications during the prepartum period affect milk yield, metabolism and offspring performance of dairy and beef cattle (Haisan et al., 2021; Hare et al., 2023), sheep (Banchero et al., 2004b) and goats (Celi et al., 2008). Exceeding energy requirements during the last stage of gestation can increase glucose and insulin concentrations (Banchero et al., 2004a; Haisan et al., 2021; Janovick et al., 2011). In addition, high-starch diets provide greater amounts of glucose as a substrate for lactose synthesis which, in turn, can increase colostrum and milk yields, as described in sheep (Banchero et al., 2004a).

In the present study, a high-starch diet prepartum did not cause increased serum glucose concentration during the prepartum period. In addition, the high-starch diet prepartum did not affect either colostrum yield or lactose percentage. As no differences were observed in circulating glucose concentrations between groups, the lack of effects on colostrum yield and lactose percentage were also expected. In agreement with these findings, Ramírez-Vera et al. (2012) reported no differences in plasma glucose concentration during the prepartum period in goats supplemented with maize. Consequently, as suggested by Hare et al. (2023), prepartum glucose partitioning to the mammary gland may already be increased during colostrogenesis, so the metabolic pathways involving glucose could be saturated before the starch supplementation. In addition, high yielding breeds are genetically programmed for body tissue mobilization in the transition period regardless of the nutritive value of the diet (Drackley et al., 2014; Ribeiro et al., 2023). These facts could explain the lack of response to the high-starch diet prepartum observed in this study.

Regarding other metabolites, the progressive increase in serum BHB concentration observed in this study before parturition can be associated to the NEB caused by late gestation and the onset of lactation as previously described by Zamuner et al. (2020) in Saanen goats. Despite

316 the present study showed an increased BHB concentration in both groups before parturition,
317 goats receiving the high-starch diet prepartum increased BHB concentrations in a lower extent
318 than the goats receiving the control diet. These results suggest that providing a high-starch diet
319 prepartum can promote a smoother transition to lactation, reducing the extent of fat
320 mobilization before parturition, contributing not only to reduce NEB, but also promoting better
321 gut adaptation to high fermentable lactation diets, reducing the incidence of metabolic diseases
322 such as ketosis or rumen acidosis around parturition.

323 Despite both experimental diets were isoproteic, the high-starch diet prepartum caused reduced
324 TP, urea and albumin concentrations. This could be attributed to different protein sources in the
325 prepartum diets, as the CON group received 100 g/d of soybean meal as part of the concentrate
326 while the HS group was fed maize exclusively. These results are in agreement with previous
327 results showing increased plasma urea concentrations in Saanen goats fed soybean meal
328 compared to goats fed other protein sources Santos et al. (2014). In addition, increasing dietary
329 starch content can impact ruminal and hind-gut microbiota (Khafipour et al., 2016; Rivera-
330 Chacon et al., 2024) affecting fermentation and nutrient digestibility and, consequently, altering
331 the absorption of aminoacids, FFA and other substrates. According to Emmanuel and Edjtehadi,
332 (1981), high levels of ammonia in the bloodstream may damage cell membranes leading to
333 impaired transport of nutrients and consequently interfere with cell metabolism. This might
334 explain not only TP and urea differences between the HS and CON groups but also the greater
335 LDH concentration observed in the CON group during the pre- and postpartum periods.

336 Exceeding dietary energy requirements prepartum seems to affect colostrum IgG concentration
337 in dairy cows, however, there is still controversy in the literature. While Springer et al. (2008)
338 found that providing high energy diets prepartum caused increased colostrum IgG
339 concentration in dairy cows, Mann et al. (2016) and Hare et al. (2023) reported lower colostrum
340 IgG concentration in dairy and beef cattle fed a high energy diet during the last month of

341 gestation. In sheep, Gallo et al. (2020) found that exceeding dietary energy requirements (i.e.,
342 10% ME kg/DM) did not affect colostrum immunoglobulin concentration. There is limited
343 literature on the effects of feeding a high-starch diet to dairy goats during the prepartum period
344 on colostrum IgG concentration. In the present study, the increased colostrum IgG
345 concentration is likely associated with either modifications in plasma IgG concentrations and
346 impaired IgG transfer from blood to colostrum (Mann et al., 2016) or modifications on the IgG
347 local synthesis (Sordillo and Nickerson, 1988; Aitken et al., 2011). However, it is still unknown
348 which mechanisms regulate these physiological pathways as colostrum IgG concentration has
349 been demonstrated to be highly variable between individual animals (Baumrucker and
350 Bruckmaier, 2014). It can be assumed that high energy diets can alter glucose metabolism,
351 inducing hormonal changes that might impact key pathways involved in colostrogenesis such
352 as the synthesis and transcytosis of immune components. Thus, high glucose concentrations
353 have been shown to alter B cells function, decreasing immunoglobulin secretion under in-vitro
354 experimental conditions (Jennbacken et al., 2013). In addition, since B cells can express insulin
355 receptors (Baumrucker et al., 2022), high energy diets could modulate their function during
356 colostrum synthesis.

357 High-starch diets are often provided at the onset of lactation to meet energy requirements for
358 milk production. However, studies focusing on feeding high-starch diets prepartum to assess
359 the subsequent lactation performance on dairy goats are scarce. Despite the benefits of
360 providing high-starch diets at the onset of lactation, abrupt changes in the dietary starch content
361 during the transition period increases the risk of acute rumen acidosis, reducing ruminal fibre
362 digestibility, ruminal acetate/propionate ratio, and increasing the concentration of circulating
363 inflammation markers which in turn can cause reduced dry matter intake and milk yield in dairy
364 cows (Emmanuel et al., 2008; Haisan et al., 2021; Hernández-Castellano et al., 2021), sheep
365 and goats (Shen et al., 2018; Zhang et al., 2024). Since the present study found no effects on

366 colostrum yield or chemical composition, no differences in milk yield and composition were
367 expected either. In fact, there are discrepancies in the literature regarding the effects of starch
368 supplementation on milk yield and composition. Thus, Tsiplakou et al. (2017) found that
369 feeding high-starch diets to dairy goats at d 90 of lactation has no effects on milk chemical
370 composition nor in casein profile, whereas Bernard et al. (2022) reported a reduction in milk
371 fat content of goats fed a high concentrate diet. In contrast, other studies described increased
372 milk yield caused by reduced dietary fibre content followed by the inclusion of cereal grains
373 (Pulina et al., 2007). The inconsistency among studies could be attributed to different starch
374 sources, timing and length of supplementation, as well as breed and management system.

375 Regarding goat kid metabolism and performance, it is known that lamb and goat kid birth BW
376 is not affected by the energy supplementation during the last weeks before parturition
377 (Banchero et al., 2004a; 2004b; Hall et al., 1992). However, some authors suggested that
378 glucose uptake by the foetus is directly proportional to the available glucose present in the dam
379 bloodstream, thus the prepartum dietary supplementation with glucose precursors could cause
380 heavier newborn animals (Battaglia & Meschia, 1988; Banchero et al., 2004a). As the high-
381 starch diet prepartum did not affect circulating glucose concentration in the present study,
382 similar birth BW between both goat kid groups was expected. In addition, exceeding dietary
383 starch during the last month of gestation did not have any impact on milk intake, which agrees
384 with previous studies performed by Celi et al. (2008).

385 In the present study, goat kids born from HS goats showed higher TP concentration after
386 colostrum intake whereas other metabolites were unaffected. Despite increased TP
387 concentrations could be associated to the increased colostrum protein content observed in those
388 goats receiving the high-starch diet prepartum, this cannot be attributed to higher IgG
389 absorption as no differences in circulating IgG concentrations were observed between goat kid
390 groups. Unfortunately, no studies have reported the effects of a high-starch diet prepartum on

391 the transfer of passive immunity in dairy goats. Despite the present study showed an increased
392 IgG concentration in colostrum from goats fed the high-starch diet prepartum, no differences
393 in plasma IgG concentrations between goat kid groups were detected. It seems that feeding
394 high quality colostrum (i.e., ≥ 20 mg/mL of IgG; Argüello et al., 2004) might saturate the
395 absorption capacity of immunoglobulins in the small intestine, resulting in no differences on
396 the immunity acquired by newborn goat kids (Besser et al., 1985; González-Cabrera et al.,
397 2024). Indeed, the apparent efficiency of absorption of IgG can vary widely, ranging from less
398 than 13.3% to greater than 40% (Rodríguez et al., 2009; Geiger, 2020). This high apparent
399 efficiency of absorption variability could explain the lack of differences in circulating IgG
400 concentrations in goat kids that received colostrum with higher IgG concentration. However,
401 the precise physiological mechanism behind these observations requires further research.

402 **CONCLUSION**

403 Feeding a prepartum high-starch diet during the last month of gestation caused increased
404 colostrum IgG concentration without affecting colostrum yield or chemical composition. The
405 prepartum high-starch diet induced changes in the metabolism of the dams, reducing the extent
406 of fat mobilization without increasing serum glucose concentrations. Despite the enhanced
407 colostrum quality, the high-starch diet prepartum did not affect the transfer of passive
408 immunity, metabolism and growth of the goat kids. These findings suggest that feeding 134%
409 DM starch requirements in late gestation increases colostrum IgG concentrations and promotes
410 a smoother transition from late gestation to the onset of lactation in dairy goats.

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DATA AVAILABILITY

The data presented in this study are available on request from the corresponding author.

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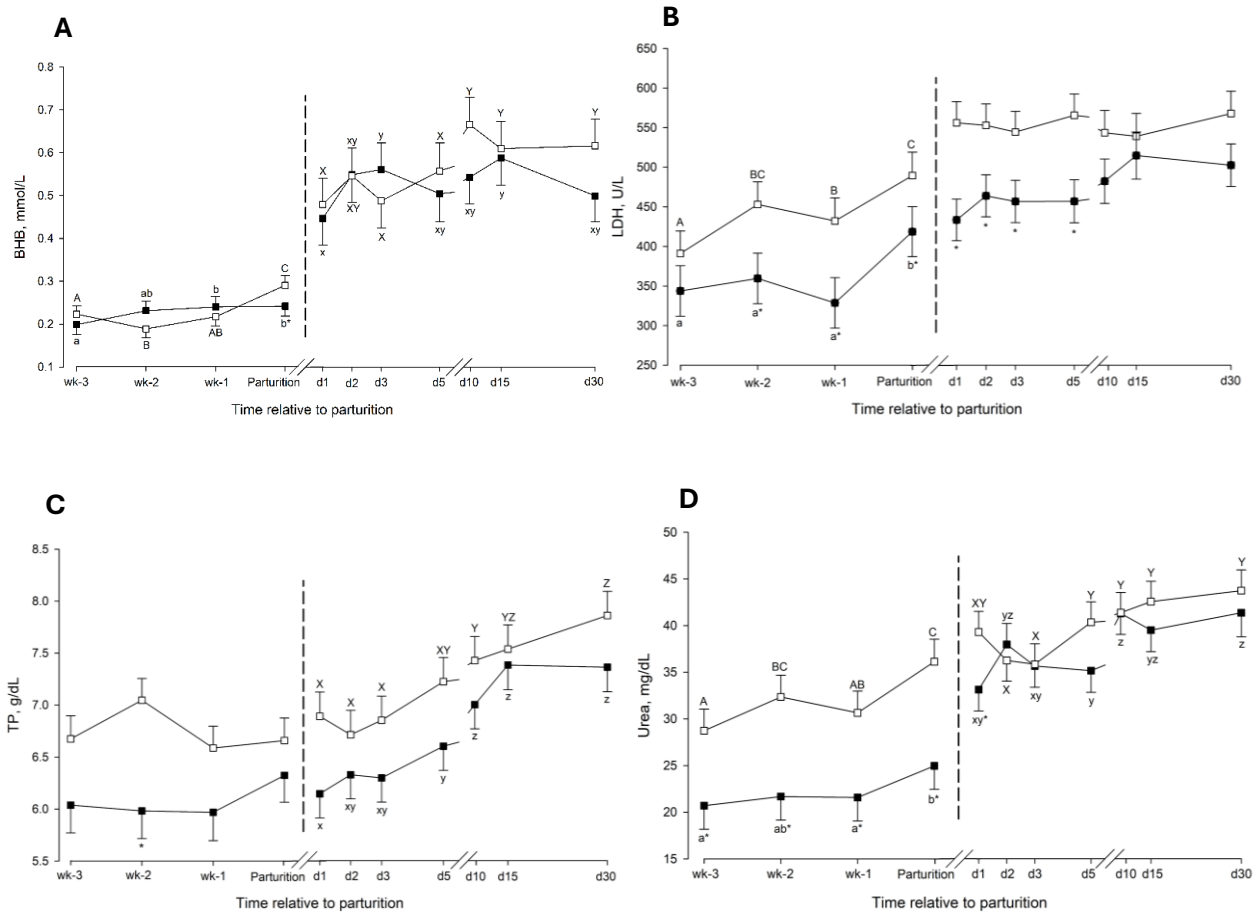
FIGURE LEGENDS

Figure 1. Serum β-Hydroxybutyrate (BHB; A), lactate dehydrogenase (LDH; B), total protein (TP; C) and urea (D) concentration in the HS (■; 134% DM starch requirements, n = 13) and CON (□; 100% DM starch requirements, n = 14) groups during the prepartum (wk -3, -2, -1 and parturition), postpartum period (d 1, 2, 3, 5, 10, 15 and 30 relative to parturition). Different superscripts (a-c) indicate significant differences ($P < 0.05$) in the HS group during the prepartum period. Different superscripts (A-C) indicate significant differences ($P < 0.05$) in the CON group during the prepartum period. Different superscripts (x-z) indicate significant differences ($P < 0.05$) in the HS group during the postpartum period. Different superscripts (X-Z) indicate significant differences ($P < 0.05$) in the CON group during the postpartum period. Significant differences between both groups are represented with (*). Data is expressed as LSM ± SEM.

Figure 2. Serum total protein concentration in goat kids born from HS goats (■; n = 25) and CON goats (□; n = 18) throughout the experimental period. Different superscripts (a-d) indicate significant differences ($P < 0.05$) in the HS group. Different superscripts (A-C) indicate significant differences ($P < 0.05$) in the CON group. Significant differences between both groups are represented with (*). Data is expressed as LSM ± SEM. TP = total protein.

656 **Figure 1. González-Cabrera et al.**



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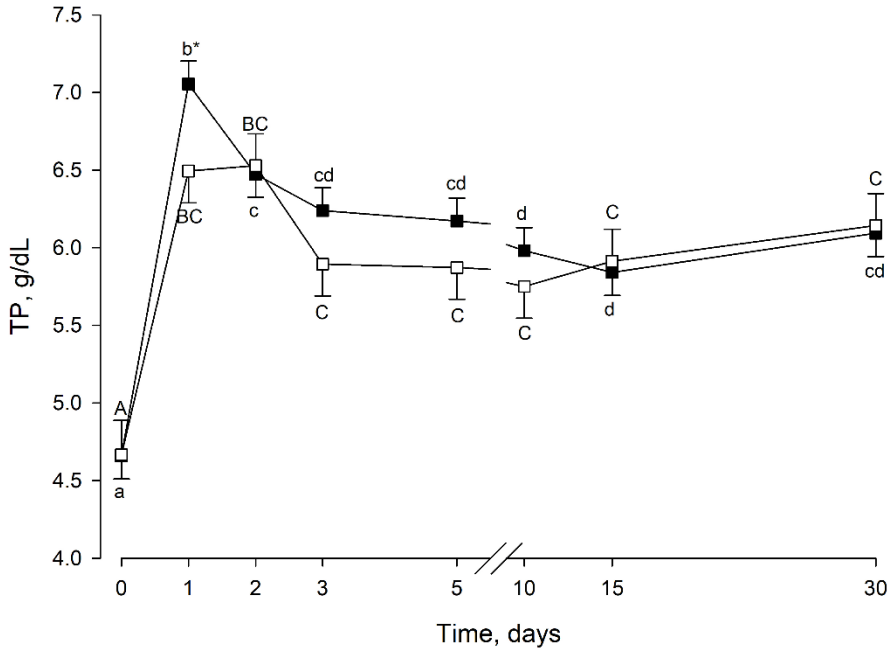
658 **Figure 2. González-Cabrera et al.**



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660 **Table 1.** Ingredients and chemical composition of experimental diets.

	Gestation			Lactation
	4th month	5th month		1st month
Group		CON	HS	
Ingredients, kg (as fed basis)				
Maize	0.69	0.55	0.75	0.65
Soybean meal (oil <5%, 46% protein + oil)	-	0.10	-	0.12
Lucerne dehydrated (16 - 18% protein)	-	-	-	0.18
Italian ryegrass hay	0.60	1.00	1.00	0.60
Lucerne hay	-	-	-	0.43
Nutrients (dry matter basis)				
Gross energy[1], kcal	4 813.0	6 143.1	6 489.1	7 457.8
CP, g	53.1	61.1	65.4	96.5
Crude fat, g	36.6	41.5	46.9	51.1
NDF, g	402.8	620.1	628.3	680.1
Starch, g	439.7	356.2	478.1	425.6
Calcium, g	2.1	3.6	3.3	7.8
Phosphorous, g	2.7	3.6	3.5	4.3

661 [1] Estimated using INRA (2018). CON = control group; HS = High-starch group; CP = Crude
662 protein; NDF = Neutral detergent fibre.

Table 2. Goat serum metabolites and plasma IgG concentration in the HS (134% DM starch requirements, n = 13) and CON (100% DM starch requirements, n = 14) groups during the prepartum period (wk -3, -2, -1) and at parturition (d 0).

	Groups			Fixed effects		
Variables	HS	CON	SEM	Diet	Time	Diet × T
IgG, mg/mL	17.1	18.0	2.70	0.533	0.723	0.406
BHB, mmol/L	0.23	0.23	0.02	0.832	<0.001	0.006
Glucose, mg/dL	43.8	40.4	2.52	0.135	0.938	0.467
FFA, mmol/L	0.34	0.35	0.04	0.793	<0.001	0.583
Calcium, mg/dL	7.1	7.6	0.16	0.047	0.299	0.606
LDH, U/L	362.7	441.5	23.81	0.039	<0.001	0.256
TP, g/dL	6.1	6.7	0.16	0.019	0.110	0.147
Urea, mg/dL	22.2	32.0	2.25	<0.001	<0.001	0.458
Albumin, g/dL	3.0	3.3	0.07	0.017	0.007	0.347

HS = High-starch group; CON = control group; T = time; IgG = immunoglobulin G; BHB = β-hydroxybutyrate; FFA = free fatty acids; LDH = lactate dehydrogenase; TP = Total protein.

668 **Table 3.** Goat serum metabolites and plasma IgG concentrations in the HS (134% DM starch
669 requirements, n = 13) and CON (100% DM starch requirements, n = 14) groups during the
670 postpartum period (d 1, 2, 3, 5, 10, 15 and 30).

	Groups			Fixed effects		
Variables	HS	CON	SEM	Diet	Time	Diet × T
IgG, mg/mL	18.8	20.0	1.00	0.414	<0.001	0.375
BHB, mmol/L	0.5	0.6	0.05	0.578	0.019	0.281
Glucose, mg/dL	42.2	44.6	2.89	0.304	0.163	0.217
FFA, mmol/L	0.5	0.5	0.08	0.750	0.154	0.200
Calcium, mg/dL	7.3	7.7	0.32	0.176	<0.001	0.220
LDH, U/L	473.0	552.8	22.23	0.019	0.456	0.323
TP, g/dL	6.7	7.2	0.20	0.093	<0.001	0.408
Urea, mg/dL	37.7	39.9	1.87	0.270	<0.001	0.028
Albumin, g/dL	3.1	3.3	0.13	0.105	<0.001	0.126

671 HS = High-starch group; CON = control group; T = time; IgG = immunoglobulin G; BHB = β-
672 hydroxybutyrate; FFA = free fatty acids; LDH = lactate dehydrogenase; TP = Total protein.

673 **Table 4.** Yield, chemical composition, SCC, Brix degrees and IgG concentration in colostrum
674 of goats from the HS (134% DM starch requirements, n = 13) and CON (100% DM starch
675 requirements, n = 14) groups at parturition (d 0).

	Groups			Fixed effect
Variables	HS	CON	SEM	Diet
Yield, kg/d	1.8	1.7	0.35	0.997
Lactose, %	2.9	2.8	0.24	0.783
Fat, %	8.8	7.0	0.88	0.150
Protein, %	14.4	14.2	1.63	0.926
Total solids, %	28.5	26.6	2.10	0.507
SCC, $\log_{10}$ cells/mL	2.7	2.8	0.19	0.678
Brix, °	25.1	23.5	1.65	0.512
IgG, mg/mL	85.4	60.5	8.39	0.047

676 HS = High-starch group; CON = control group; SCC = somatic cell count; IgG =
677 immunoglobulin G.

678 **Table 5.** Yield, chemical composition, SCC, Brix degrees and IgG concentration in transition
679 milk of goats from the HS (134% DM starch requirements, n = 13) and CON (100% DM starch
680 requirements, n = 14) groups on d 1, 2 and 3 after parturition.

	Groups			Fixed effects		
Variables	HS	CON	SEM	Diet	Time	Diet × T
Yield, kg/d	1.7	1.7	0.13	0.984	<0.001	0.464
Lactose, %	4.0	4.0	0.12	0.890	<0.001	0.170
Fat, %	6.1	6.8	0.33	0.085	0.807	0.931
Protein, %	6.9	7.3	0.35	0.432	<0.001	0.256
Total solids, %	17.9	19.2	0.52	0.100	<0.001	0.381
SCC, log10 cells/mL	2.9	2.9	0.13	0.977	0.094	0.403
Brix, °	13.8	15.1	0.67	0.151	<0.001	0.228
IgG, mg/mL	18.0	14.1	3.22	0.304	<0.001	0.252

681 HS = High-starch group; CON = control group; SCC = somatic cell count; IgG = immunoglobulin G.

682 **Table 6.** Yield, chemical composition, SCC and Brix degrees and IgG concentration in whole
683 milk of goats from the HS (134% DM starch requirements, n = 13) and CON (100% DM starch
684 requirements, n = 14) groups on d 5, 10, 15 and 30 after parturition.

	Groups			Fixed effects		
Variables	HS	CON	SEM	Diet	Time	Diet × T
Yield, kg/d	2.4	2.2	0.13	0.418	0.404	0.901
Lactose, %	4.6	4.6	0.05	0.934	0.429	0.872
Fat, %	4.4	4.6	0.14	0.350	<0.001	0.514
Protein, %	4.0	4.1	0.08	0.395	<0.001	0.237
Total solids, %	14.0	14.3	0.15	0.158	<0.001	0.222
SCC, log10 cells/mL	2.4	2.5	0.11	0.772	0.073	0.538
Brix, °	11.1	11.3	0.11	0.238	<0.001	0.638
IgG, mg/mL	1.7	2.0	0.15	0.115	<0.001	0.876

685 HS = High-starch group; CON = control group; SCC = somatic cell count; IgG = immunoglobulin G.

686 **Table 7.** Body weight, individual milk intake, rectal temperature, serum metabolites and
687 plasma IgG concentrations in goat kids born from goats from the HS (dams fed 134% DM
688 starch requirements, n = 25) and CON (dams fed 100% DM starch requirements, n = 18)
689 groups.

	Groups			Fixed effects		
Variables	HS	CON	SEM	Diet	Time	Diet × T
BW, kg	4.5	4.4	0.28	0.741	<0.001	0.440
MI, mL	975.8	907.1	59.76	0.338	<0.001	0.087
RT, °C	39.1	39.2	0.05	0.150	<0.001	0.929
Albumin, g/dL	2.8	2.8	0.05	0.490	<0.001	0.070
Glucose, mg/dL	71.8	73.2	2.74	0.674	<0.001	0.862
Calcium, mg/dL	10.4	10.3	0.13	0.468	<0.001	0.090
TP, g/dL	6.1	5.9	0.11	0.232	<0.001	0.011
LDH, U/L	773.5	832.7	31.38	0.117	<0.001	0.780
Urea, mg/dL	44.3	45.5	1.13	0.507	<0.001	0.288
IgG, mg/mL	12.7	12.4	0.93	0.796	<0.001	0.166

690 HS = goat kids from dams fed a high-starch diet prepartum (134% DM starch requirements); CON =
691 goat kids from dams fed a control diet prepartum (100% DM starch requirements); T = time; MI =
692 Individual milk intake; RT = Rectal temperature; TP = Total protein; LDH = lactate dehydrogenase;
693 IgG = Immunoglobulin G.

Capítulo 5

Chapter 5

La administración de lipopolisacáridos intramamarios en el momento del parto mejora la concentración de inmunoglobulinas en el calostro

Intramammary administration of lipopolysaccharides at parturition enhances immunoglobulin concentration in goat colostrum

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RESUMEN

La modulación de la calostrogénesis en pequeños rumiantes constituye una potente herramienta para garantizar una correcta transferencia de inmunidad pasiva. Este estudio tiene como objetivo aumentar la permeabilidad de la barrera sangre-leche administrando lipopolisacáridos (LPS) vía intramamaria a cabras en el momento del parto para modular la composición del calostro. Veinte cabras multíparas gestantes de la raza Majorera fueron asignadas aleatoriamente a uno de los dos grupos experimentales. El grupo LPS (n = 10) recibió una administración intramamaria (IA) de solución salina (2 ml) que contenía 50 µg de LPS de *Escherichia coli* (O55:B5) en cada cuarterón de la ubre en el momento del parto, mientras que el grupo control (n = 10) recibió una IA que contenía una solución salina (2 ml) sin LPS. Se registró la temperatura rectal (RT) y se tomó una muestra de sangre en el momento del parto y antes de la IA. Además, se midió la RT y se tomaron muestras de sangre, calostro y leche en los días 0,125 (3 horas), 0,5 (12 horas), 1, 2, 4, 7, 15 y 30 relativos a la IA. Se determinaron las concentraciones de inmunoglobulina G (IgG) y M (IgM) en plasma y las concentraciones de β-hidroxibutirato, glucosa, calcio, ácidos grasos libres, lactato deshidrogenasa y proteína total en suero. Asimismo, se registró la producción de calostro y leche, la composición química, el recuento de células somáticas (SCC) y las concentraciones de IgG e IgM. Las cabras del grupo LPS mostraron una RT más alta en los días 0,125 y 0,5 relativos a la IA en comparación con el grupo control, indicando una respuesta inflamatoria sistémica y de corta duración. Sin embargo, los metabolitos en el suero y las concentraciones plasmáticas de IgG e IgM no se vieron afectadas por la IA. La producción de calostro y leche, así como la composición química, no se vieron influenciados por la IA, excepto el porcentaje de lactosa en la leche que fue menor en el grupo LPS en comparación con el grupo control (4,3 ± 0,08 y 4,6 ± 0,08%, respectivamente). Tal y como cabría esperar, el SCC en el calostro fue mayor en el grupo LPS que en el grupo control (3,5 ± 0,09 y 3,1 ± 0,09 células × 10^6/ml, respectivamente), indicando un posible aumento de células inmunes en el calostro debido a la respuesta desencadenada por el LPS. De manera similar, el grupo LPS mostró concentraciones más altas de IgG e IgM en el calostro que el grupo control (45,3 ± 4,43 y 28,0 ± 4,47 mg/ml, 0,8 ± 0,08 y 0,5 ± 0,08 mg/ml, respectivamente), reflejando una mayor transferencia de

inmunoglobulinas como respuesta al estímulo inmune ocasionado por el LPS. En conclusión, el aumento de la permeabilidad de la barrera sangre-leche debido a la respuesta inmune causada por la administración intramamaria de lipopolisacáridos podría explicar los resultados obtenidos en el presente ensayo, el cual sienta las bases para futuros estudios sobre la modulación de la calostrogénesis.

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Intramammary administration of lipopolysaccharides at parturition enhances immunoglobulin concentration in goat colostrum

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ABSTRACT

In newborn ruminants, transfer of passive immunity is essential to obtain protection against pathogens. This study aimed to increase the permeability of the blood-milk barrier using intramammary lipopolysaccharides (**LPS**) in goats at parturition to modulate colostrum composition. Twenty multiparous *Majorera* dairy goats were randomly allocated in one of the two experimental groups. The LPS group (n = 10) received an intramammary administration (**IA**) of saline (2 mL) containing 50 μg of LPS from *Escherichia coli* (O55:B5) in each half udder at parturition. The control group (n = 10) received an IA of saline (2 mL). Rectal temperature (**RT**) was recorded, and a blood sample was collected at parturition (before IA). In addition, RT was measured, and blood and colostrum/milk samples were collected on day (d) 0.125 (3 hours), 0.5 (12 hours), 1, 2, 4, 7, 15 and 30 relative to the IA. Goat plasma immunoglobulin G (**IgG**) and M (**IgM**) and serum β-hydroxybutyrate, glucose, calcium, free fatty acids, lactate dehydrogenase and total protein concentrations were determined. Colostrum and milk yields as well as chemical composition, somatic cell count (**SCC**), IgG and IgM concentrations were measured. The MIXED procedure (SAS 9.4) was used, and the model included the IA, time, and the interaction between both fixed effects. Statistical significance was set as $P < 0.05$. Goats from the LPS group showed higher RT on d 0.125, 0.5 and 4 relative to the IA compared to the control group ($P_{IA \times Time} = 0.007$). Goat serum biochemical variables and plasma IgG and IgM concentrations were not affected by the IA. Colostrum and milk yield as well as chemical composition were not affected by the IA, except for milk lactose percentage that was lower in the LPS group compared to the control group (4.3 ± 0.08 and 4.6 ± 0.08%, respectively $P_{IA} = 0.026$). Colostrum SCC was higher in the LPS group than in the control group (3.5 ± 0.09 and 3.1 ± 0.09 cells × 10^6/mL, respectively; $P_{IA} = 0.011$). Similarly, milk SCC increased in the LPS group compared to the control group ($P_{IA} = 0.004$). The LPS group showed higher IgG ($P_{IA} = 0.044$) and IgM ($P_{IA} = 0.037$) concentrations on colostrum than the control group (31.9 ± 4.8 and 19.0 ± 4.8 mg/mL, 0.8 ± 0.08 and 0.5 ± 0.08 mg/mL, respectively). No differences in milk IgG and IgM concentrations between groups were observed. In conclusion, the IA of LPS at parturition increases RT, SCC and IgG and IgM concentrations in colostrum without affecting either yield or chemical composition.

Implications

Dairy goat industry faces important losses caused by high perinatal mortality. Therefore, providing good quality colostrum to goat kids is essential. This study offers a novel and unique approach to improve colostrum quality, based on the application of intramammary lipopolysaccharides at parturition. This strategy can increase immune components (i.e., immunoglobulins) in colostrum, and consequently enhance the performance and immune status of goat kids during the first weeks of life, reducing the incidence of transfer of passive immunity failure and the use of antibiotics, which has a positive effect on animal welfare and the economic benefit of producers.

Introduction

Mammals have developed different strategies to provide immunity to their offspring. In ruminants, due to the placental structure,

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the transfer of passive immunity strictly depends on early colostrum intake after birth to provide immunization until newborns are able to synthesize their own immune components (Castro et al., 2005). Colostrum contains a complex mixture of bioactive molecules (Barrington et al., 2001; Hernández-Castellano et al., 2014), with immunoglobulin G (**IgG**) the most abundant (McGrath et al., 2015; Puppel et al., 2019).

In the mammary gland, the blood-milk barrier is responsible for preventing an indiscriminate exchange of components between blood and milk. Although, colostrum synthesis is mostly based on active mechanisms such as endocytosis or transcytosis, immune components such as IgG can be also transferred into colostrum through leaky tight junctions (Baumrucker and Bruckmaier, 2014; Hernández-Castellano et al., 2018). During mastitis (i.e., inflammation of the mammary gland), the tight junctions between epithelial mammary cells are damaged and the integrity of the blood-milk barrier is reduced, increasing the passage of plasma proteins, antibodies, and leukocytes among others from blood to milk (Nguyen and Neville, 1998; Bruckmaier and Wellnitz, 2017).

Reduced integrity of the blood-milk barrier has been used to study the inflammatory response of the udder under different challenges (Wellnitz et al., 2011; Vernay et al., 2012; Wall et al., 2018). In dairy cows, the intramammary administration of oxytocin (Wall et al., 2016a), progesterone (Nguyen and Neville, 1998) and some nonsteroidal anti-inflammatory drugs such as selective and not selective cyclooxygenase (Sintes et al., 2020) reduce the integrity of the blood-milk barrier, whereas prolactin (Flint and Gardner, 1994) and glucocorticoids such as cortisol (Herve et al., 2017) or prednisolone (Wellnitz et al., 2014) stabilize it preventing leakage.

Lipopolysaccharides (**LPS**) are cell wall components of Gram-negative bacteria that play an important role in host–pathogen interactions with the innate immune system (Maldonado et al., 2016). The intramammary administration (**IA**) of LPS can mimic a sterile mastitis, and indirectly, modifies colostrum and milk composition (González-Cabrera et al., 2022). This study hypothesizes that the IA of LPS at parturition increases the permeability of the blood-milk barrier, enhancing the transfer of immune components, such as IgG, from blood to colostrum and milk. Therefore, this study aimed to use an IA of LPS at parturition to improve colostrum and milk composition in dairy goats.

Material and methods

Experimental design

The present experiment was carried out on an experimental farm located in the Veterinary Faculty at the Universidad de Las Palmas de Gran Canaria (Arucas, Spain).

Twenty pregnant *Majorera* dairy goats within the second and fourth lactation with an average BW 65.7 ± 2.80 kg were used in this study. All animals were visually healthy before they were included in the experiment. From the fourth month of gestation to the first month of lactation, animals were fed according to the guidelines published by *L'Institut National de la Recherche Agronomique* (Sauvant et al., 2018) and had free access to water and to mineral blocks (i.e., Na, 36.0 g/kg; Ca, 1.00 g/kg; Mg, 0.6 g/kg; $MnSO_4$, 312 mg/kg $FeSO_4$, 200 mg/kg; Na_2SeO_3, 33 mg/kg; Ca (IO_3), 24 mg/kg; $(CH_3COO)_2Co^*4H_2O$, 8 mg/kg). Feed composition during late gestation (i.e., fourth and fifth month) and first month of lactation is described in Table 1.

The experimental period started at parturition and lasted until week 4 postpartum. At parturition, each goat was randomly allocated to one of the two experimental groups. Goat kids were immediately removed after birth and were not allowed to suck colostrum from the dams. The LPS group (n = 10) received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5, Sigma-Aldrich, St. Louis, MO) diluted in 2 mL of saline solution 0.9% in each half udder immediately after parturition and 3 hours (h) before first milking, and therefore in full udders. Similarly, goats from the control group (n = 10) received an IA with 2 mL of 0.9% saline solution in each half udder without LPS. Teat openings were disinfected with 70% ethanol, and then, a 1.0 × 130 mm sterile catheter (Buster Cat Catheter, Kruuse, Norway) was used for the IA.

Table 1
Feed composition of the diets used daily during late gestation (i.e., fourth and fifth month) and first month of lactation in the experimental goats.

Item	Gestation		Lactation
	4th month	5th month	1st month
Ingredients, kg (DM basis)			
Maize	0.69	0.65	0.65
Soybean meal (oil < 5%, 46% protein + oil)	–	–	0.13
Lucerne dehydrated (16–18% protein)	–	–	0.18
Italian ryegrass hay	0.60	0.68	0.60
Lucerne hay	–	–	0.43
Nutrients (DM basis)			
Gross energy, kcal	5 612.3	5 783.2	8 678.5
CP, g	102.5	104.5	266.9
Crude fat, g	224.4	252.8	431.1
NDF, g	487.3	539.2	814.6
Starch, g	510.2	478.3	492.8
Calcium, g	2.9	3.3	12.7
Phosphorous, g	7.5	7.3	9.5

Blood, colostrum, and milk sampling

Blood samples were collected immediately after parturition and before the IA (0 h) and then on day (d) 0.125 (3 h), 0.5 (12 h), 1, 2, 4, 7, 15 and 30 relative to parturition. Samples were collected from the jugular vein using 20 mL syringes (Injekt Braun, Braun, Germany) and 20G needles (Sterican Braun, Braun, Germany). Blood was immediately transferred to EDTA-K2 tubes (BD Vacutainer®, UK) for plasma collection, and serum tubes (SEROTUB, Deltalab™, Spain). Plasma tubes were placed on wet ice immediately after collection and centrifuged at 2 190 × *g* for 5 min at 4 °C (Hettich-Zentrifugen, Universal 32 R, Tuttlingen, Germany) within 30 minutes. Serum tubes were stored at room temperature for 2 h and then centrifuged at 2 190 × *g* for 5 min at 4 °C. Both plasma and serum were aliquoted in 1.5 mL Eppendorf Tubes®.

Colostrum and milk samples were collected on d 0.125, 0.5, 1, 2, 4, 7, 15 and 30 postpartum. Goats were milked completely in a double 12-stall parallel milking parlour (Alfa Laval Iberia SA, Madrid, Spain) equipped with recording jars (3.5 L ± 5%) using the procedure described by Torres et al. (2013).

All samples (i.e., plasma, serum, colostrum, and milk) were stored at −20 °C until laboratory analyses were performed.

Variables

Immunoglobulin G (IgG) and M (**IgM**) concentrations in blood plasma, colostrum and milk were measured using commercial ELISA kits (Bethyl Laboratories, Montgomery, TX, USA). The intra-assay coefficients of variation were 5.8 and 4.8%, respectively. The inter-assay coefficients of variation were 5.1 and 2.9%, respectively. Concentrations of β-hydroxybutyrate (**BHB**; 137019910930, DiaSys Diagnostics, Holzheim, Germany), glucose (GN45126, RAL laboratories, Barcelona, Spain), calcium (GN12125, RAL laboratories, Barcelona, Spain), lactate dehydrogenase (**LDH**; GN42125, RAL laboratories, Barcelona, Spain), free fatty acids (**FFA**;

157819910935, DiaSys Diagnostics, Holzheim, Germany) and total proteins (**TP**; GN46125, RAL laboratories, Barcelona, Spain) were measured for blood serum using an automatic spectrophotometer (METROLAB 2300GL, RAL laboratories, Barcelona, Spain). The intra-assay coefficients of variation were 0.56, 2.10, 1.10, 1.92, 1.07, and 0.90% respectively. The inter-assay coefficients of variation were 2.15, 3.09, 2.16, 3.10, 1.15, and 1.43%, respectively. Further information regarding these laboratory techniques can be found in Supplementary Material S1.

Colostrum and milk chemical composition (fat, protein, lactose, and total solids) were determined using a MilkoScan™ Mars (FOSS IBERIA, Spain). Colostrum samples were diluted 1:4 (v/v) using deionized water based on the procedure described by Spina et al. (2021) and Soufleri et al. (2023). Colostrum and milk somatic cell count (**SCC**) were determined using a DeLaval cell counter (DeLaval, Tumba, Sweden). Samples with a SCC $\geq$ 3 000 10^3 cells/mL were diluted 1:5 (v/v) with saline solution as described by Kawai et al. (2013).

In addition, rectal temperature (**RT**) was measured at parturition before the IA (0 h) and at the milking parlour before each milking using a digital thermometer (Beurer, Germany).

Statistical analysis

The SAS POWER procedure (version 9.4, SAS Institute Inc., Cary, NC, USA) was used to determine the minimum number of animals needed in this study to identify significant differences at the 5% level with a power of 80%. Based on this, the minimum number of animals per group was ten (10). The main variable used in this procedure was IgG concentration in goat colostrum. According to Hernández-Castellano et al. (2016), the IgG concentration in *Majorera* goat colostrum is 41.1 mg/mL with a SD of 5.65 mg/mL, with a significant difference considered if IgG concentration differs > 5.7 mg/mL between groups.

Data were analysed using the MIXED PROCEDURE of SAS. The model included the IA (LPS vs. control), time (from parturition to d 30 postpartum) and the interaction between both (IA $\times$ Time) as fixed effects. The animal (i.e., goat) was considered as an individual subject and time as a repeated measure. The Tukey test was used to determine significant differences ($P < 0.05$) between groups. The homogeneity of the variance and the normality of the residuals were estimated graphically using PROC UNIVARIATE. Data for variables that did not meet these criteria were log-transformed ($\log_{10}$) to get a normal distribution of residues and homogeneity. Results are presented as Least Square Means ± SEM. Results that were log-transformed and then back-transformed are presented as Mean [Minimum and Maximum].

Results

In this study, the gestation length was 150 ± 2 days with an average litter size of 2.3 ± 0.56 kids. No clinical signs of mastitis (i.e., swollen, warmth, or pain in the udder) were observed in the LPS and control groups after the IA. No differences were observed in the individual DM intake among groups on either the fourth and fifth month before parturition (2.2 ± 0.21 and 2.2 ± 0.25 kg DM, respectively; $P > 0.05$) or the first month of lactation (2.2 ± 0.34 kg DM; $P > 0.05$). Similarly, no differences in BW were observed among groups on either the fourth and fifth month before parturition (68.8 ± 2.44 and 69.1 ± 2.23, respectively; $P = 0.390$) or the first month of lactation (67.9 ± 2.97$P = 0.489$).

Variables analysed in colostrum

Colostrum yield and chemical composition (i.e., lactose, protein, fat, and total solids) were not affected by the IA (Table 2; $P_{IA} \geq 0.065$) but were affected by time (Table 2; $P_{Time} \leq 0.002$). Colostrum yield increased from d 0.125 to d 2 (1.9 ± 0.22 and 2.4 ± 0.21 kg, respectively). In addition, lactose percentage increased from d 0.125 to d 2 (2.8 ± 0.14 and 3.8 ± 0.16%, respectively) whereas protein percentage decreased (10.2 ± 0.57 and 7.0 ± 0.62%, respectively). Fat and total solids increased from d 0.125 (8.8 ± 0.56 and 23.7 ± 1.0%, respectively) to d 0.5 (9.8 ± 0.64 and 30.0 ± 1.07%, respectively) decreasing afterwards until d 1 (5.6 ± 0.56 and 17.2 ± 0.94%, respectively) to increase again at d 2 (8.0 ± 0.64 and 26.1 ± 1.06%, respectively).

In contrast, SCC (Table 2; Fig. 1) was higher in the LPS group compared to the control group (3.5 ± 0.09 and 3.1 ± 0.09 $\log_{10}$ cells/mL, respectively; $P_{IA} = 0.011$). Similarly, both colostrum IgG concentration (Table 2; Fig. 2A) and IgG total mass (Table 2) were higher ($P_{IA} \leq 0.044$) in the LPS group (31.9 ± 4.80 mg/mL and 51.8 ± 6.22 g, respectively) compared to the control group (19.0 ± 4.80 mg/mL and 29.8 ± 6.23 g, respectively). In both groups, colostrum IgG concentration decreased from d 0.125 to d 2 relative to the IA (51.7 ± 4.74 mg/mL and 8.7 ± 4.86 mg/mL, respectively; $P_{Time} < 0.001$). Furthermore, IgM concentration (Table 2; Fig. 2B) and IgM total mass (Table 2) were also affected by the IA ($P_{IA} \leq 0.037$), with higher concentration in the LPS group (0.8 ± 0.08 mg/ml and 1.4 ± 0.23 g, respectively) than in the control group (0.5 ± 0.08 mg/mL and 0.8 ± 0.22 g, respectively). Colostrum IgM concentration also decreased from d 0.125 to d 2 relative to the IA (1.1 ± 0.08 mg/mL and 0.3 ± 0.08 mg/mL, respectively; $P_{Time} < 0.001$).

Variables analysed in milk

Milk yield was not affected by either the IA ($P_{IA} = 0.733$) or time ($P_{Time} = 0.513$). Protein, fat, and total solids percentages as well as IgG and IgM concentrations and total mass were not affected by the IA (Table 3; $P_{IA} \geq 0.309$). However, lactose percentage was affected by the IA as the LPS group showed lower values than control group (Table 3; 4.3 ± 0.08 and 4.6 ± 0.08%, respectively; $P_{IA} = 0.026$). Chemical composition was affected by time (Table 3; $P_{Time} < 0.001$). Protein, fat, and total solids percentages decreased from d 4 (5.2 ± 0.19, 5.3 ± 0.19, and 15.5 ± 0.29%, respectively) to d 30 (3.9 ± 0.19, 3.7 ± 0.19, and 13.2 ± 0.27%, respectively) while lactose percentage increased (4.2 ± 0.09 and 4.7 ± 0.09%, respectively). Milk SCC (Table 3; Fig. 1) was higher in the LPS group compared to the control group (2.9 ± 0.11 and 2.6 ± 0.11 $\log_{10}$ cells/mL, respectively; $P_{IA} = 0.004$). In both groups, SCC decreased from d 4 to d 30 (2.9 ± 0.11 and 2.6 ± 0.11 log10 cells/mL; $P_{Time} = 0.045$).

Rectal temperature and variables analysed in blood

A two-way interaction between the IA and time ($P_{IA \times Time} = 0.007$) was observed for RT (Table 4; Fig. 3). Rectal temperature increased in the LPS group from parturition (0 h) to d 0.125 relative to the IA (38.9 ± 0.16 °C and 39.6 ± 0.16 °C, respectively), decreasing afterwards until d 15 (38.4 ± 0.15 °C) and increasing again on d 30 relative to the IA (38.8 ± 0.15 °C). In the control group, RT decreased progressively after the IA to d 30 (38.9 ± 0.15 °C and 38.4 ± 0.15 °C, respectively).

No differences between groups were detected in plasma IgG and IgM concentrations (Table 4; $P_{IA} = 0.446$, $P_{IA} = 0.243$, respectively). However, IgG concentration in both groups increased from parturition to d 0.125 (5.7 [4.5–7.2] and 10.4 [8.2–13.2] mg/dL, respectively $P_{Time} < 0.001$) decreasing constantly until d 1 and then increasing until d 15 (4.5 [3.6–5.7] and 13.0 [10.5–16.2] mg/dL, respectively). In addition, IgM concentrations were also affected by time increasing from d 1 to d 15 (1.5 ± 0.12 and 2.0 ± 0.12 mg/mL, respectively; $P_{Time} < 0.001$) and then decreasing until d 30 (1.9 ± 0.12 mg/mL).

Table 2
Yield, chemical composition, and immunoglobulin concentrations in colostrum (d 0.125, 0.5, 1 and 2) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	1.9	1.8	0.22	0.792	0.002	0.462
Lactose, %	3.2	3.5	0.15	0.111	0.002	0.204
Fat, %	7.5	8.6	0.42	0.065	<0.001	0.862
Protein, %	8.8	8.2	0.60	0.393	<0.001	0.641
Total solids, %	24.1	24.4	0.72	0.637	<0.001	0.378
SCC, log_{10} cells/mL	3.5	3.1	0.09	0.011	0.161	0.169
IgG, mg/mL	31.9	19.0	4.80	0.044	<0.001	0.515
IgG total mass, g	51.8	29.8	6.23	0.002	<0.001	0.644
IgM, mg/mL	0.8	0.5	0.08	0.037	<0.001	0.798
IgM total mass, g	1.4	0.8	0.23	0.010	<0.001	0.590

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS.; IA = intramammary administration; IA × Time = Interaction IA × Time; SCC = somatic cell count; IgG = Immunoglobulin G; IgM = Immunoglobulin M.

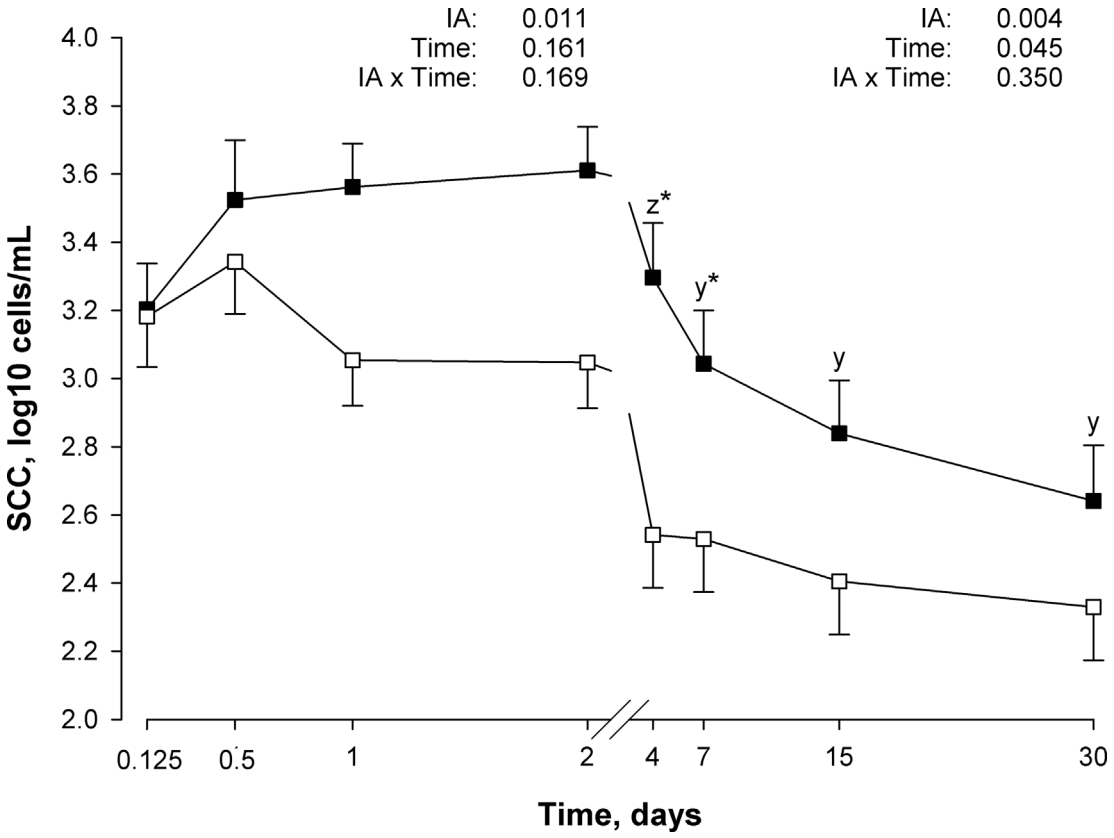

Fig. 1. Somatic cell count (SCC) in colostrum (d 0.125, 0.5, 1 and 2 relative to the IA) and milk (d 4, 7, 15 and 30 relative to the IA) throughout the experimental period in goats from the LPS (■) and control (□) groups. Different letters (z-y) indicate significant differences ($P < 0.05$) in milk in the LPS group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

Serum BHB, Glucose, Calcium, LDH, FFA and TP were not affected by the IA (Table 4; $P_{IA} \geq 0.087$) but were affected by time ($P_{Time} \leq 0.004$). Serum BHB concentrations decreased progressively from parturition to the end of the experimental period (1.2 [0.9–1.6] mmol/L and 0.6 [0.4–0.8] mmol/L, respectively). Glucose concentrations decreased from parturition to d 2 (90.1 [80.0–101.4] mg/dL and 37.8 [33.6–42.6] mg/dL, respectively) and then increased constantly until d 30 (49.6 [44.5–55.3] mg/dL). Similarly, calcium concentrations decreased from parturition to d 2 (8.5 ± 0. 24 mg/dL and 8.0 ± 0.24 mg/dL, respectively) and increased progressively until the end of the experimental period (9.4 ± 0.24 m g/dL). Serum LDH activity increased constantly from parturition to d 15 (427.4 ± 28.58 U/L and 515.0 ± 28.58 U/L, respectively) showing a decrease on d 30 (510.3 ± 28.58 U/L). Serum FFA concentrations decreased progressively from parturition to the end of the experimental period (1.4 ± 0.08 mmol/L and 0.5 ± 0.08 mmol/L, respectively). Total protein concentrations decreased from parturition to d 1 (6.3 ± 0.18 g/dL and 5.9 ± 0.18 g/dL, respectively) and then increased constantly until d 30 (7.1 ± 0.18 g/dL).

Discussion

The IA of LPS to mimic a mastitis caused by Gram-negative bacteria has been used in dairy species since the 1980s. Some of these studies assessed the effect of LPS administration on mammary

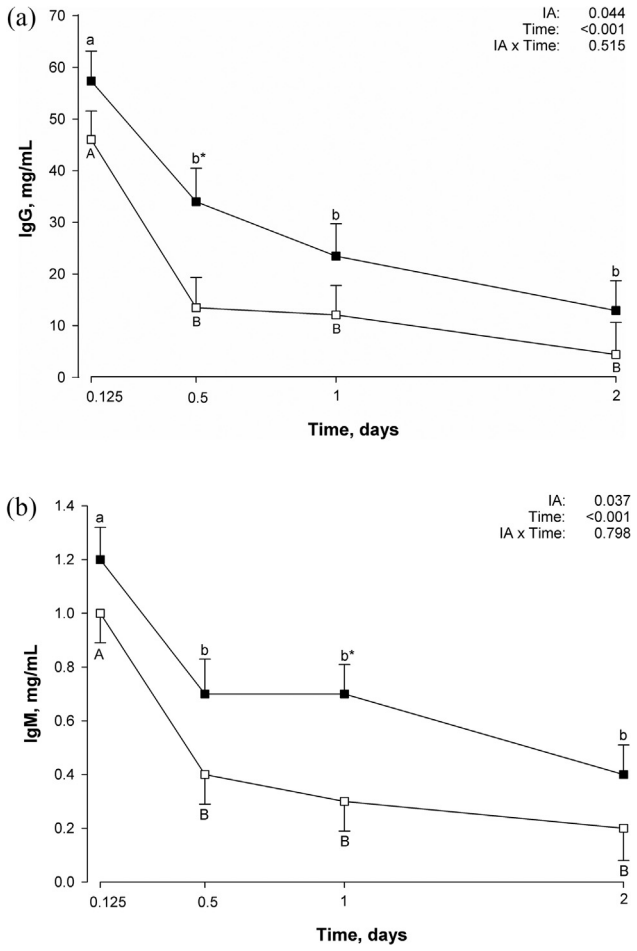

Fig. 2. Immunoglobulin G (A, IgG) and immunoglobulin M (B, IgM) in colostrum (d 0.125, 0.5, 1 and 2 relative to the IA) of goats from the LPS (■) and control (□) groups. Different letters (a-b) indicate significant differences ($P < 0.05$) in the LPS group. Different letters (A-B) indicate significant differences ($P < 0.05$) in the control group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

blood flow (Dhondt et al., 1977), mastitis development (Johnzon et al., 2018), systemic responses (Sintes et al., 2020), drug efficacy (Wall et al., 2016b), and milk composition (Wellnitz and Bruckmaier, 2021). However, the use of an IA of LPS to intentionally enhance dairy goat colostrum and milk composition has never been tested.

In the present study, the IA of LPS did not affect colostrum yield or chemical composition but enhanced IgG and IgM concentrations compared to the animals that received the IA of saline without LPS. In dairy cows, the IA of LPS can modify the blood-milk barrier permeability, enhancing the transfer of immune components, in particular IgG, within the first 3 h after the IA (Wellnitz et al., 2013; Lehmann et al., 2013). In this study, 50 μg of LPS were applied to dairy goats immediately after parturition, 3 h before first milking. Previous studies have demonstrated that the milk ejection reflex and the associated oxytocin release occurs in response to suckling or milking (Hernandez et al., 2002; Belo and Bruckmaier, 2010). Therefore, to avoid triggering the onset of lactogenesis and subsequent changes in colostrum composition, no samples were collected before the first milking at 3 h. Both the dose of LPS and the timing of administration used in the present study could explain the results obtained. Higher doses of intramammary LPS (i.e., 100 μg) in empty udders can cause greater and faster tissue damage, promoting immune responses and composition changes shortly after administration (Werner-Misof et al., 2007b). In this study, the IA of LPS was performed immediately after parturition, and therefore, in full udders. The presence of colostrum in the udder may reduce the interaction between LPS molecules and the mammary tissue, causing a delayed immune response which could explain the different effects observed in previous studies. Despite the permeability of the blood-milk barrier was not determined in the present study, it is likely that the increased concentration of immunoglobulins (i.e., IgG and IgM) in colostrum might be caused by leakage of components from blood to the mammary gland during inflammation. In mice, the IA of LPS can induce changes in claudins which are essential transmembrane proteins to maintain blood-milk barrier permeability (Kobayashi et al., 2013). Colostrum immunoglobulins can be either synthesized in the mammary gland or transferred from the bloodstream during colostrogenesis (Hernández-Castellano et al., 2018). Although IgG subclasses (i.e., IgG_1 and IgG_2) have been widely described in bovine colostrum (Barrington et al., 1997; Stelwagen et al., 2009), they have not been fully investigated in goats as no specific antibodies are available for this determination. Wall et al. (2015) described that these subclasses are transferred to colostrum and milk by different mechanisms during mastitis, showing that IgG_1 is actively transported by FcRn receptors whereas IgG_2 is more likely to diffuse passively through the blood-milk barrier. Furthermore, inflammatory agents such as cytokines can induce an over-expression of FcRn receptors promoting greater IgG_1 transfer to the mammary gland (Jiang et al., 2016). These findings suggest a potential effect of the IA of LPS on the mammary gland immune response and, therefore, could be used to intentionally modulate the permeability of the blood-milk barrier to increase colostrum and milk immune components in dairy species.

Besides the effect of the IA of LPS on colostrum immunoglobulin concentrations, an increased SCC in colostrum and milk was also observed. Several studies have demonstrated that the intensity of the immune response is dose-related (Van Oostveldt et al., 2002), being more intense at high doses as the greater damage to the tight junctions causes increased flow of inflammatory cells into milk (Baumert et al., 2009). In fact, Werner-Misof et al., (2007a) reported that SCC in bovine mammary glands treated with different LPS doses (i.e., 6.25, 12.5, 25, 50, and 100 μg in 10 mL of saline) reaches the maximum value within the first 12 h post-treatment according to the applied dose. Baumert et al. (2009) also detected an increased SCC in dairy cows at 10 h after the IA, but these differences were no longer observed after 24 h. In contrast, the present study demonstrates that the effect of IA on LPS seems to be extended in dairy goats, even after the LPS molecule has been removed, as differences among groups were still present 48 h after the IA. Similarly, Salama et al. (2020) observed increased SCC in dairy goats 72 h after the IA. Differences of SCC among studies might be explained by the dose, timing of LPS administration and the species used in the study. Low doses of intramammary LPS in dairy cows did not induce clinical signs of inflammation or SCC increase (Werner-Misof et al., 2007b). In addition, high doses of LPS applied in full udders might result in lower or delayed responses to inflammation than in empty udders, which are directly exposed to LPS. Intramammary administration of LPS before or after milking can determine different timing in the inflammation process and consequently can modulate the immune cell migration to the udder.

Although no changes were observed in colostrum chemical composition, the IA of LPS caused reduced lactose percentage in milk. This change in chemical composition could be caused by tissue damage and modifications on the blood-milk barrier permeability during inflammation, affecting the synthesis and transfer

Table 3
Yield, chemical composition, and immunoglobulin concentrations in milk (d 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	2.5	2.4	0.18	0.733	0.513	0.842
Lactose, %	4.3	4.6	0.08	0.026	<0.001	0.927
Fat, %	4.3	4.5	0.15	0.309	<0.001	0.065
Protein, %	4.4	4.3	0.16	0.676	<0.001	0.161
Total solids, %	14.1	14.4	0.22	0.450	<0.001	0.602
SCC, log_{10} cells/mL	2.9	2.5	0.11	0.004	0.045	0.350
IgG, mg/mL	0.8	0.9	0.10	0.468	0.035	0.159
IgG total mass, g	1.9	2.0	0.17	0.899	0.004	0.111
IgM[1], μg/mL	105.0 [90.2–122.2]	96.3 [82.8–112.1]	–	0.458	<0.001	0.258
IgM total mass, g	0.3	0.2	0.03	0.310	<0.001	0.304

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS; IA = intramammary administration; IA × Time = Interaction IA × Time; SCC = somatic cell count; IgG = Immunoglobulin G; IgM = Immunoglobulin M.
[1] Mean, minimum and maximum obtained from the log10 transformation.

Table 4
Concentrations of plasma immunoglobulins (IgG and IgM) and serum metabolites, as well as rectal temperature (d 0.125, 0.5, 1, 2, 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P*-value		
Variables	LPS	Control		IA	Time	IA × Time
IgG,[1] mg/mL	8.4 [7.2–9.7]	7.7 [6.7–9.0]	–	0.446	<0.001	0.744
IgM, mg/mL	1.6	1.8	0.11	0.243	<0.001	0.775
BHB,[1] mmol/L	0.8 [0.6–1.1]	1.0 [0.7–1.3]	–	0.611	0.002	0.729
Glucose,[1] mg/dL	48.2 [40.2–54.3]	48.4 [45.3–51.8]	–	0.883	<0.001	0.430
Calcium, mg/dL	8.6	8.5	0.13	0.347	<0.001	0.699
LDH, U/L	490.1	456.6	23.1	0.313	0.004	0.302
FFA, mmol/L	0.9	0.9	0.05	0.782	<0.001	0.667
TP, g/dL	6.5	6.2	0.14	0.087	<0.001	0.976
RT, °C	39.0	38.7	0.07	0.002	<0.001	0.007

Abbreviations: LPS = group that received an IA consisting of 50 μg of LPS (*Escherichia coli* serotype O55:B5) diluted in 2 mL of saline solution 0.9% in each half udder; the control group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS; IA = intramammary administration; IA × Time = Interaction IA × Time; IgG = Immunoglobulin G; IgM = Immunoglobulin M; BHB = β-hydroxybutyrate; LDH = lactate dehydrogenase; FFA = free fatty acids; TP = total protein; RT = rectal temperature.
[1] Mean, minimum and maximum, obtained from log10 transformation.

of components. Reduced lactose percentages in milk during mastitis have been associated with increased SCC (Antanaitis et al., 2021), increased transfer of lactose to the bloodstream (Chedly et al., 2010), and the use of lactose by pathogens as a source of energy (Silanikove et al., 2014). Changes in lactose percentages can be also associated with negative energy balance after parturition (Ptak et al., 2012; dos Santos et al., 2019). Similarly, Salama et al. (2020) did not observe differences in milk yield between LPS-treated and untreated mammary glands but found greater milk protein content and lower lactose percentages in LPS-challenged udder-halves of *Murciano-Granadina* goats. In addition, other authors observed lower milk yields during the first 24 h after the LPS challenge in dairy ewes and cows (Castro-Costa et al., 2014; Shangraw et al., 2020), as well as lower lactose content, supporting that induced mastitis can affect milk composition. The milk secretion mechanism in dairy goats (i.e., apocrine secretion) compared to cows and ewes (i.e., merocrine secretion) could explain the different effects of LPS on milk yield in these species (Paape and Capuco, 1997; Souza et al., 2012). During mastitis, casein degradation causes the release of active peptides that down-regulate milk secretion in cows, ewes and goats (Silanikove et al., 2000; Leitner et al., 2008). However, the greater content of casein and plasmin activity in cow and ewe milk compared to goat milk could also explain the lack of variation in goat milk yield after the IA of LPS.

Despite the changes observed in colostrum and milk composition, as well as the increased RT caused by the IA, no differences in plasma IgG and IgM concentrations were observed during the entire experimental period. These findings are in agreement with the results described by Lehmann et al. (2013), who found no variation on serum IgG concentration in cows that received an IA of LPS. These findings would indicate a short-term systemic response to the locally induced infection which was not sufficient to increase IgG and IgM concentrations on the bloodstream. Similarly, Salama et al. (2020) and Gross et al. (2020) observed an increase of RT in LPS-challenged dairy goats (i.e., within the first 8 h after the IA) and Holstein cows (i.e., within the first 5 h after the IA), respectively.

Although the present study shows no changes in blood serum metabolites associated to the IA of LPS, some variations were detected throughout the experimental period. Thus, serum BHB was elevated at parturition and decreased progressively until d 30 relative to the IA. According to Baird and Pugh (2002), blood concentrations of BHB above 0.8 mmol/L are indicative of negative energy balance in ewes, so these results might be explained by the high energy demand at the onset of lactation. For the same reason, glucose and FFA were also elevated immediately after parturition.

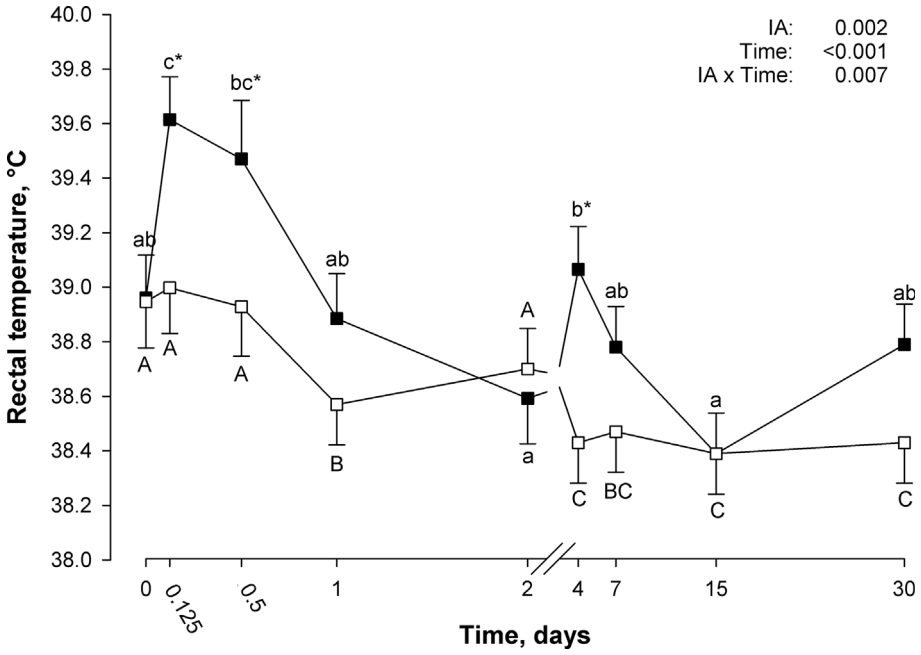

Fig. 3. Rectal temperature throughout the experimental period in goats from the LPS (■) and control (□) groups. Different letters (a–c) indicate significant differences ($P < 0.05$) over time in the LPS group. Different letters (A–C) indicate significant differences ($P < 0.05$) over time in the control group. Significant differences between both groups are represented with (*). Abbreviations: IA = Intramammary administration. Data are expressed as least square means ± SEM.

Conclusion

The intramammary administration of lipopolysaccharides in dairy goats at parturition can modify colostrum composition, increasing immunoglobulin concentrations (i.e., IgG and IgM) and somatic cell count. These results might be associated with the increased blood-milk barrier permeability and immune response caused by the intramammary administration of lipopolysaccharides. This study could set the baseline for future studies on the modulation of the blood-milk barrier at parturition to enrich goat colostrum quality under experimental conditions. However, further studies must be conducted to determine the suitability of LPS as a tool to increase colostrum quality in practical conditions such as dairy farms.

Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.animal.2024.101082.

Ethics approval

The experiment was approved by the Ethical Committee for Animal Experimentation of the Universidad de Las Palmas de Gran Canaria following the national legislation (OEBA-ULPGC; Procedure 27/2021).

Data and model availability statement

None of the data were deposited in an official repository. The data presented in this study are available on request from the corresponding author.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use any artificial intelligence-assisted technologies in the writing process.

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Declaration of interest

None.

Acknowledgments

None.

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Corrigendum

Corrigendum to "Intramammary administration of lipopolysaccharides at parturition enhances immunoglobulin concentration in goat colostrum" [Animal 18 (2) (2024) 101082]

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In the published paper, the authors reported incorrect IgG concentrations due to an error in the dilution factor applied to calculate the final concentration. Therefore, the authors claim that this is an unintentional mistake and does not influence the conclusion of the publication.

The authors apologise for this error and any inconvenience caused.

The errors are corrected as follows:

In the abstract, the statement "The LPS group showed higher IgG (P_{IA} = 0.044) and IgM (P_{IA} = 0.037) concentrations on colostrum than the control group (31.9 ± 4.8 and 19.0 ± 4.8 mg/mL, 0.8 ± 0.08 and 0.5 ± 0.08 mg/mL, respectively)" should be replaced by "The LPS group showed higher IgG (P_{IA} = 0.044) and IgM (P_{IA} = 0.037) concentrations on colostrum than the control group (45.3 ± 4.43 and 28.0 ± 4.47 mg/mL, 0.8 ± 0.08 and 0.5 ± 0.08 mg/mL, respectively)".

In the results, the statement "Similarly, both colostrum IgG concentration (Table 2; Fig. 2A) and IgG total mass (Table 2) were higher ($P_{IA} \leq 0.044$) in the LPS group (31.9 ± 4.80 mg/mL and 51. 8 ± 6.22 g, respectively) compared to the control group (19.0 ± 4.80 mg/mL and 29.8 ± 6.23 g, respectively). In both groups, colostrum IgG concentration decreased from d 0.125 to d 2 relative to the IA (51.7 ± 4.74 mg/mL and 8.7 ± 4.86 mg/mL, respectively; $P_{Time} < 0.001$)" should be replaced by "Similarly, both colostrum IgG concentration (Table 2; Fig. 2A) and IgG total mass (Table 2) were higher ($P_{IA} \leq 0.044$) in the LPS group (45.3 ± 4.43 mg/mL and 77. 7 ± 9.16 g, respectively) compared to the control group (28.0 ± 4.47 mg/mL and 44.7 ± 9.35 g, respectively). In both groups, colostrum IgG concentration decreased from d 0.125 to d 2 relative to the IA (75.8 ± 4.68 mg/mL and 11.9 ± 5.16 mg/mL, respectively; $P_{Time} < 0.001$)". The statement "However, IgG concentration in both groups increased from parturition to d 0.125 (5.7 [4.5–7.2] and 10.4 [8.2–13.2] mg/dL, respectively $P_{Time} < 0.001$) decreasing constantly until d 1 and then increasing until d 15 (4.5 [3.6–5.7] and 13.0 [10.5–16.2] mg/dL, respectively)" should be replaced by "However, IgG concentration in both groups increased from parturition to d 0.125 (9.4 [7.4–11.9] and 15.4 [12.0–19.6] mg/dL, respectively $P_{Time} < 0.001$) decreasing constantly until d 1 and then increasing until d 15 (6.8 [5.3–8.6] and 19.5 [15.6–24.4] mg/dL, respectively)".

In addition, authors did not include the unit in the statement "Similarly, no differences in BW were observed among groups on either the fourth and fifth month before parturition (68.8 ± 2.44 and 69.1 ± 2.23, respectively; P = 0.390) or the first month of lactation (67.9 ± 2.97 P = 0.489)", thus it should be added as follow "Similarly, no differences in BW were observed among groups on either the fourth and fifth month before parturition (68.8 ± 2.44 and 69.1 ± 2.23 kg, respectively; P = 0.390) or the first month of lactation (67.9 ± 2.97 kg; P = 0.489).

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In Table 2, the data in bold has been replaced as follows:

Table 2. Yield, chemical composition, and immunoglobulin concentrations in colostrum (d 0.125, 0.5, 1 and 2) of goats from the LPS (n = 10) and control groups (n = 10). Data is expressed as least square means.

	Groups		SEM	Fixed effects, *P-value*		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	1.9	1.8	0.22	0.792	0.002	0.462
Lactose, %	3.2	3.5	0.15	0.111	0.002	0.204
Fat, %	7.5	8.6	0.42	0.065	<0.001	0.862
Protein, %	8.8	8.2	0.60	0.393	<0.001	0.641
Total solids, %	24.1	24.4	0.72	0.637	<0.001	0.378
SCC, $\log_{10}$ cells/mL	3.5	3.1	0.09	0.011	0.161	0.169
IgG, mg/mL	**45.3**	**28.0**	**4.47**	0.044	<0.001	0.515
IgG total mass, g	**77.7**	**44.7**	**9.35**	0.002	<0.001	0.644
IgM, mg/mL	0.8	0.5	0.08	0.037	<0.001	0.798
IgM total mass, g	1.4	0.8	0.23	0.010	<0.001	0.590

In Table 3, the data in bold has been replaced as follows:

Table 3. Yield, chemical composition, and immunoglobulin concentrations in milk (d 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

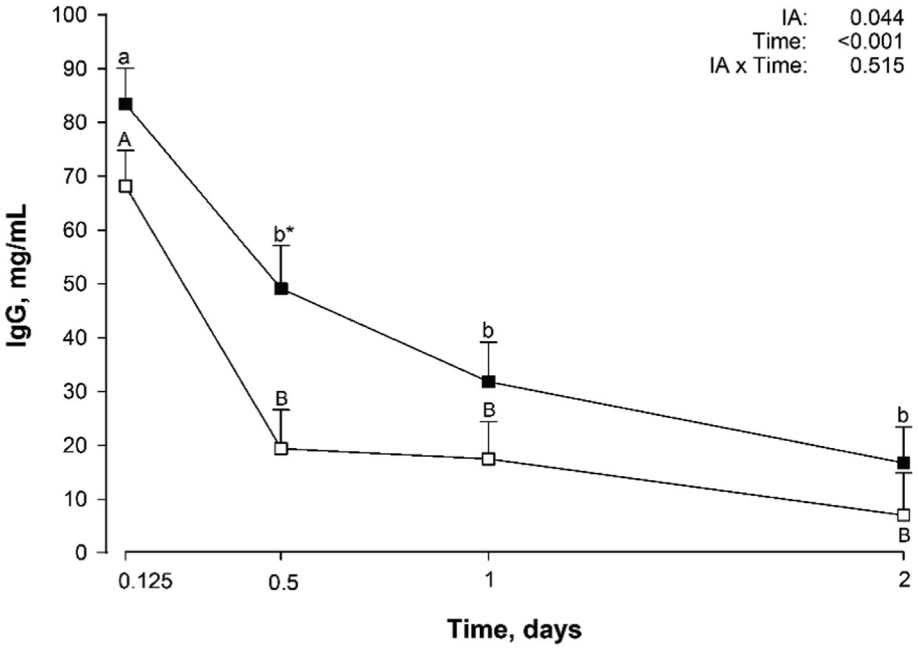
	Groups		SEM	Fixed effects, *P-value*		
Variables	LPS	Control		IA	Time	IA × Time
Yield, kg	2.5	2.4	0.18	0.733	0.513	0.842
Lactose, %	4.3	4.6	0.08	0.026	<0.001	0.927
Fat, %	4.3	4.5	0.15	0.309	<0.001	0.065
Protein, %	4.4	4.3	0.16	0.676	<0.001	0.161
Total solids, %	14.1	14.4	0.22	0.450	<0.001	0.602
SCC, $\log_{10}$ cells/mL	2.9	2.5	0.11	0.004	0.045	0.350
IgG, mg/mL	**1.1**	**1.3**	**0.10**	0.468	0.035	0.159
IgG total mass, g	**2.9**	**3.1**	**0.25**	0.899	0.004	0.111
IgM[1], μg/mL	105.0 [90.2–122.2]	96.3 [82.8–112.1]	–	0.458	<0.001	0.258
IgM total mass, g	0.3	0.2	0.03	0.310	<0.001	0.304

In Table 4, the data in bold has been replaced as follows:

Table 4. Concentrations of plasma immunoglobulins (IgG and IgM) and serum metabolites, as well as rectal temperature (d 0.125, 0.5, 1, 2, 4, 7, 15 and 30) of goats from the LPS (n = 10) and control groups (n = 10). Data are expressed as least square means.

	Groups		SEM	Fixed effects, *P-value*		
Variables	LPS	Control		IA	Time	IA × Time
IgG[1], mg/mL	**12.8 [11.3–14.5]**	**11.6 [10.3–13.1]**	–	0.446	<0.001	0.744
IgM, mg/mL	1.6	1.8	0.11	0.243	<0.001	0.775
BHB[1], mmol/L	0.8 [0.6–1.1]	1.0 [0.7–1.3]	–	0.611	0.002	0.729
Glucose[1], mg/dL	48.2 [40.2–54.3]	48.4 [45.3–51.8]	–	0.883	<0.001	0.430
Calcium, mg/dL	8.6	8.5	0.13	0.347	<0.001	0.699
LDH, U/L	490.1	456.6	23.1	0.313	0.004	0.302
FFA, mmol/L	0.9	0.9	0.05	0.782	<0.001	0.667
TP, g/dL	6.5	6.2	0.14	0.087	<0.001	0.976
RT, °C	39.0	38.7	0.07	0.002	<0.001	0.007

Fig 2. (a) should be replaced by:



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Capítulo 6

Chapter 6

La administración de lipopolisacáridos intramamarios en el momento del parto no afecta a la inmunidad adquirida de los cabritos

Intramammary administration of lipopolysaccharides at parturition does not affect the transfer of passive immunity in goat kids

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RESUMEN

En los rumiantes recién nacidos, la transferencia de inmunidad pasiva es esencial para obtener una adecuada protección frente a patógenos. De este modo, el presente estudio pretende evaluar el efecto de alimentar a cabritos recién nacidos con calostro obtenido tras la administración intramamaria (IA) de LPS de *Escherichia coli* (O55:B5) a cabras en el momento del parto sobre el crecimiento, el estado metabólico e inmune durante el primer mes de vida. Los cabritos fueron pesados al nacimiento (d 0) e inmediatamente asignados al grupo LPS (n = 15) o control (n = 21) en función del grupo experimental de la madre. Tal y como se detalla en el Capítulo 5, estos cabritos procedían de 20 cabras multíparas asignadas al grupo LPS el cual recibió una IA de solución salina (2 ml) que contenía 50 µg de LPS en cada cuarterón de la ubre; o al grupo control, el cual recibió una IA con solución salina (2 ml) sin LPS. Los cabritos recibieron individualmente calostro materno, equivalente al 10% del peso corporal al nacimiento, dividido en 2 tomas (a las 3 y 12 h relativas al nacimiento). Posteriormente, fueron alimentados dos veces al día con lactoreemplazante comercial *ad libitum*. Se tomaron muestras de sangre los días 0, 1, 2, 4, 7, 15, 21 y 30 después del nacimiento y se determinó el consumo individual, la temperatura rectal (RT) y el peso corporal los días 7, 15, 21 y 30 de vida. Los consumos de ambos grupos fueron similares, excepto el día 7 relativo al nacimiento, en el que el grupo LPS mostró un mayor consumo que el grupo control (910,5 ± 69,77 y 683,9 ± 59,64 ml, respectivamente). Aunque se desconoce la razón de esta diferencia, no se observaron cambios en el peso corporal a lo largo del período experimental concluyendo que el aumento del consumo de manera puntual no compromete el crecimiento de los cabritos. Por otro lado, el consumo de calostro obtenido de las madres tratadas con LPS no tuvo efecto sobre la RT de los cabritos, lo cual indicaría, que la proporción de LPS vehiculizada en el calostro no fue suficiente para desencadenar una respuesta inflamatoria en los cabritos. Además, el consumo de este calostro no generó diferencias en las concentraciones plasmáticas de IgG e IgM, por lo que, a pesar del efecto positivo de la IA sobre la concentración de inmunoglobulinas en el calostro, la transferencia de inmunidad pasiva no se vio potenciada. En conclusión, alimentar con calostro obtenido de cabras tratadas con una administración intramamaria de lipopolisacáridos en el momento del parto no tiene consecuencias

negativas en el bienestar de los cabritos. Si bien en el presente estudio este calostro no influyó en el crecimiento, el estado metabólico ni a la transferencia de inmunidad pasiva en los cabritos, esta estrategia podría ser usada para mejorar la transferencia de inmunidad pasiva en cabras que produzcan calostros de baja calidad.

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Intramammary administration of lipopolysaccharides at parturition does not affect the transfer of passive immunity in goat kids

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ABSTRACT

This study evaluated the effect of feeding colostrum obtained from an intramammary administration (IA) of LPS from *Escherichia coli* (O55:B5) to dairy goats at parturition, on goat kid performance, biochemical parameters (i.e., calcium, lactate dehydrogenase, glucose, total proteins, albumin, and urea) and immune status (i.e., IgG and IgM) during the first month of life. At birth, goat kids were weighted (d 0) and immediately allocated into either the LPS group (n = 15) or the control (CON) group (n = 21) based on the experimental group of the dam. At parturition, 20 multiparous dairy goats were allocated in 1 of the 2 experimental groups (LPS vs. CON). The LPS group received an IA of saline solution (2 mL) containing 50 µg of LPS in each half udder whereas goats in the CON group received an IA of saline solution (2 mL) without LPS. Goat kids were bottle-fed dam colostrum equivalent to 10% of the birth BW divided in 2 meals (i.e., at 3 and 12 h relative to birth), and then fed twice daily with milk replacer ad libitum. Individual milk intake (MI) and BW were recorded on d 7, 15, 21 and 30 of life. Blood samples were collected on d 0, 1, 2, 4, 7, 15, 21 and 30 after birth. Data were analyzed using the MIXED procedure of SAS (9.4; SAS Institute Inc.). The model included IA, time (T), and their interaction (IA × T) as fixed effects, and sex and litter size as random effects. Both groups showed similar MI, except on d 7 relative to birth as the LPS group showed higher MI than the CON group (910.5 ± 69.77 and 683.9 ± 59.64 mL, respectively; mean ± SEM). No differences in BW or rectal temperature were observed between groups, neither in plasma IgG nor IgM concentrations. Despite the IA did not affect calcium, glucose, LDH, total protein, and albumin concentrations an interaction between the IA and T was observed for urea concentration, showing the LPS group higher urea concentrations than the CON group on d 0 (20.1 ± 1.34 and 20.0 ± 1.25 mg/dL, respectively). In conclusion, feeding colostrum from goats that received an IA of LPS at parturition does not affect goat kid performance, plasma immunoglobulin concentrations and serum metabolites during the first month of life.
Key words: immune, dairy, growth, performance

INTRODUCTION

During gestation, ruminant placenta does not allow the sufficient transfer of immune components to the fetus (Stelwagen et al., 2009; Hernández-Castellano et al., 2015b). Thus, goat kids are born without enough maternal immune factors, relying on colostrum consumption to face infectious and noninfectious challenges after birth (Besser and Gay, 1994; Weaver et al., 2000). In addition to nutrients, colostrum contains other bioactive molecules such as hormones, immunoglobulins, and antimicrobial peptides that have an important role in the protection and the muscle and gastrointestinal development of the newborn animal (Pakkanen and Aalto, 1997; Hernández-Castellano et al., 2014).

Colostrum quality has traditionally been determined by the immunoglobulin concentration, mainly IgG. In goat colostrum, the IgG concentration is about 2.4 times greater than in blood serum (Micusan and Bord, 1977). There are 2 IgG subclasses (i.e., IgG_1 and IgG_2). The IgG_1 is mainly transferred from the bloodstream by a receptor mediated pathway and represents about 95% to 98% of total colostrum IgG (Korhonen et al., 2000). The IgG_2 is mostly recycled within the tissue but can be also transferred to colostrum in much lower rates (Baumrucker et al., 2021). Both isotypes are also synthesized by immune cells in the mammary gland, increasing its synthesis during natural and induced inflammation (Wellnitz et al., 2013; Ezzat Alnakip et al., 2014). In addition to im-

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The list of standard abbreviations for JDS is available at adsa.org/jds-abbreviations-24. Nonstandard abbreviations are available in the Notes.

munoglobulins, colostrum also contains a wide variety of nonimmunoglobulin proteins that play a fundamental role in the activation of the immune system. In ruminants, colostrum quality is directly associated with newborn survival (Hernández-Castellano et al., 2015a) and depends on multiple factors such as species (Kessler et al., 2019), the nutritional status of the dam (Banchero et al., 2004a,b), management system (Castro et al., 2011), and udder health (Alcindo et al., 2022), among others.

During either natural or induced udder inflammation (i.e., mastitis), the selective transfer of IgG_1 to colostrum is reduced, whereas there is a marked increase of other proteins, such as IgG_2 or serum albumin (Lascelles A.K., 1979) and an infiltration of blood neutrophils, T-lymphocytes, and macrophages, which release cytokines (i.e., TNF-a, IL-1, IL-2, or IL-6) within the mammary tissue (Burton and Erskine, 2003; Kusebauch et al., 2018). This inflammatory response can lead to changes in the permeability of the blood-milk barrier (**BMB**) causing the leakage of blood components into milk (Wall et al., 2016; Bruckmaier and Wellnitz, 2017).

Gram-negative bacteria are ubiquitous pathogens commonly involved in mastitis (Wellnitz et al., 2011). Their cell wall contains molecules such as LPS that have been widely used in Holstein cows (Lehmann et al., 2013; Gross et al., 2020), sheep (Castro-Costa et al., 2014) and goats (Salama et al., 2020; González-Cabrera et al., 2024) to stimulate the immune system and simulate a sterile mastitis. In fact, changes in the milk proteome in response to an intramammary administration (**IA**) of LPS in dairy goats have been characterized, showing that antimicrobial and acute phase proteins such as cathelicidin-1 and -3, lactoferrin, haptoglobin, and serum amyloid A are increased in milk after the IA of LPS (Olumee-Shabon et al., 2013). In addition, other studies have shown that feeding milk containing LPS (i.e., 12 µg/kg of BW) to dairy calves does not trigger a systemic immune response (Samarasinghe et al., 2020).

Currently, the effect of feeding colostrum from goats challenged with an IA of LPS at parturition on goat kid performance, immune status, and blood metabolites has not been evaluated. In this study, it is hypothesized that feeding colostrum from goats treated with an IA of LPS at parturition enhances the immunity acquired by the offspring. Therefore, this study aimed to assess the effect of feeding colostrum from goats challenged with an IA of LPS at parturition on goat kid performance, immune status, and blood metabolites.

MATERIALS AND METHODS

Experimental Design

The present experiment was conducted in the experimental farm located in the Veterinary Faculty at the Universidad de Las Palmas de Gran Canaria (Arucas, Spain). The experiment was approved by the Ethical Committee for Animal Experimentation (OEBA-ULPGC; Procedure 28/2021).

The experimental design has been previously described in González-Cabrera et al. (2024). In brief, 20 multiparous *Majorera* dairy goats were randomly assigned to 1 of the 2 experimental groups (LPS vs. control [**CON**]). Goats from the LPS group received an IA consisting of 50 µg of LPS (*Escherichia coli* serotype O55:B5, Sigma-Aldrich, St. Louis, MO) diluted in 2 mL of saline solution 0.9% in each half udder immediately after parturition, whereas goats from the CON group received an IA with 2 mL of 0.9% saline solution in each half udder without LPS. Teat openings were disinfected with 70% ethanol and then a 1.0 × 130 mm sterile catheter (Buster Cat Catheter, Kruuse, Norway) was used for the IA.

In this study, the average litter size was 2.31 ± 0.56 (mean ± SEM) kids. Single- and twin-born goat kids with a birth BW >2.3 kg were enrolled in the experiment, which started at birth and finished at wk 4 of life. All animals were visually healthy and immediately removed from dams before colostrum suckling. Thirty-six goat kids were allocated into the LPS group (n = 15) or the CON group (n = 21) immediately after birth based on the experimental group of the dam. Each animal was bottle-fed with colostrum (10% of the birth BW) milked from the dam 3 h after the IA of LPS in 2 meals (i.e., at 3 and 12 h relative to birth). After that, animals were fed twice daily with a commercial milk replacer formulated for goat kids (Bacilactol Cabritos, Saprogal, La Coruña, Spain; 95.5% DM, 23.6% CP, and 22.7% ether extract) at 16% (wt/wt) according to Argüello et al. (2004a).

Blood Sampling

Blood samples were collected immediately after birth before colostrum intake (d 0) and then on d 1, 2, 4, 7, 15, 21, and 30 relative to birth. Samples were taken via jugular venipuncture with 5-mL syringes (Injekt Braun, Braun, Germany) and 22-gauge needles (Sterican Braun, Braun, Germany). Samples were immediately transferred to EDTA-K2 tubes (BD Vacutainer, United Kingdom) for plasma collection, and serum tubes (Serotub, Deltalab, Spain). Plasma tubes were placed on wet ice immediately after collection and centrifuged at 2,190 × *g* for 5 min at 4°C (Hettich-Zentrifugen, Universal 32 R, Tuttlingen, Germany). Serum tubes were stored at room temperature for 2 h and then centrifuged at 2,190 × *g* for 5 min at 4°C. Both plasma and serum were aliquoted in 1.5-mL Eppendorf tubes (Flex-Tube, Eppendorf, Germany) and stored at −20°C until laboratory analysis.

Variables

Rectal temperature (**RT**) and BW were recorded on d 0, 7, 15, 21, and 30 relative to birth. Individual milk intake (**MI**) was recorded on d 7, 15, 21, and 30 relative to birth. Blood plasma IgG and IgM concentrations were measured using commercial ELISA kits (Bethyl Laboratories, Montgomery, TX). The intra-assay CV were 5.4% and 4.3%, respectively. The interassay CV were 5.3% and 2.8%, respectively. Concentrations of glucose (GN45126, RAL laboratories, Barcelona, Spain), calcium (GN12125, RAL laboratories, Barcelona, Spain), lactate dehydrogenase (**LDH**; GN42125, RAL laboratories, Barcelona, Spain), total proteins (GN46125, RAL laboratories, Barcelona, Spain), albumin (GN86125, RAL laboratories, Barcelona, Spain) and urea (GN70125, RAL laboratories, Barcelona, Spain) were measured on blood serum using an automatic spectrophotometer (METROLAB 2300GL, RAL laboratories, Barcelona, Spain). The intra-assay CV were 2.10%, 1.10%, 1.92%, 0.90%, 0.50%, and 2.79%, respectively. The interassay CV were 3.09%, 2.16%, 3.10%, 1.43%, 0.80%, and 2.65% respectively.

Statistical Analysis

Data were analyzed using the MIXED procedure of SAS (version 9.4, SAS Institute Inc., Cary, NC). The model included the IA (LPS vs. CON), time (**T**; from birth to d 30 of life), and their interaction (IA × T) as fixed effects, and litter size and sex as random effects. The animal (goat kid) was considered as an individual subject and T as a repeated measure. The Bonferroni test was used to determine significant differences ($P < 0.05$). The homogeneity of the variance and the normality of the residuals were estimated graphically using PROC UNIVARIATE. Data for variables that did not meet these criteria were log-transformed ($\log_{10}$) to get normal distribution of residues and homogeneity. Results are presented as LSM ± SEM. Results that were log-transformed and then back-transformed are presented as mean (minimum and maximum).

RESULTS

The present results should be considered in the context of the companion article (González-Cabrera et al., 2024) that reported differences between the colostrum obtained from the LPS and the CON group. Briefly, goats from the LPS group showed greater SCC in colostrum than the CON group (3.5 ± 0.09 and 3.1 ± 0.09 cells 10^6/mL, respectively). Similarly, the LPS group showed higher colostrum IgG and IgM concentrations (45.3 ± 4.43 and 0.8 ± 0.08 mg/mL, respectively) than the CON group (28.0 ± 4.50 and 0.5 ± 0.08 mg/mL, respectively). However, the IA of LPS did not affect colostrum chemical composition (i.e., fat, protein, lactose, and TS).

In the present study, an interaction between IA and T was observed for MI (Table 1; Figure 1; $P = 0.002$). Goat kids from the LPS group showed higher MI than the CON group on d 7 (836.8 ± 94.35 and 764.3 ± 72.13 mL, respectively), whereas no differences were observed over the rest of the experiment. Neither BW nor RT were affected by the IA (Table 1; $P_{IA} \geq 0.172$), but both were affected by T ($P < 0.001$). Body weight increased progressively from birth (d 0) to d 30 (3.0 ± 0.20 and 7.0 ± 0.20 kg, respectively), along with RT, which also increased from d 0 to d 30 (38.7 ± 0.07 and 39.3 ± 0.06°C, respectively).

Plasma IgG concentration in goat kids was not affected by the IA (Table 1; Figure 2A; $P_{IA} = 0.096$). but was affected by T ($P < 0.001$). Immunoglobulin G concentration increased from birth (d 0) to d 4 (0.9 ± 1.40 and 12.8 ± 1.38 mg/mL, respectively), then decreased progressively until d 15 (9.6 ± 1.40 mg/mL) and no differences were observed for the rest of the experimental period. Similarly, plasma IgM concentration was not affected by the IA (Table 1; Figure 2B; $P_{IA \times T} = 0.300$). However, IgM concentration increased from birth (d 0) to d 1 (10.7, range 8.4−13.7, and 1,035.6, range 623.4–1,720.1 µg/mL, respectively) to decrease constantly until d 30 (284.4 [172.2–469.8] µg/mL).

Calcium, glucose, LDH, total protein and albumin concentrations in goat kids (Table 1) were not affected by the IA ($P_{IA} \geq 0.075$) but were affected by T ($P < 0.001$) except for calcium concentration ($P_T = 0.232$). Glucose concentration increased progressively from birth (d 0) to d 30 (36.4 ± 5.94 and 107.9 ± 4.40 g/dL, respectively). Serum LDH activity increased from birth (d 0) to d 1 (523.5 ± 66.78 and 636.9 ± 67.36 U/L, respectively) and then decreased until d 4 (366.3 ± 67.92 U/L) to increase progressively until d 30 (840.7 ± 65.69 U/L). Similarly, total protein concentration increased from d 0 to d 1 (4.3 ± 0.16 and 5.6 ± 0.16 g/dL, respectively), decreasing until d 15 (4.7 ± 0.15 g/dL) and remaining constant until the end of the experimental period. Albumin concentration decreased from birth (d 0) to d 4 (2.3 ± 0.08 and 1.9 ± 0.08 g/dL, respectively) and then increased constantly until d 30 (2.6 ± 0.08 g/dL). In addition, an interaction between the IA and T was observed for urea concentration (Figure 3E; $P = 0.001$). Goat kids from the LPS group showed higher urea concentrations than the CON group on d 0 (20.1 ± 1.34 and 20.0 ± 1.25 mg/dL, respectively). However, no differences were observed between groups for the rest of the experimental period.

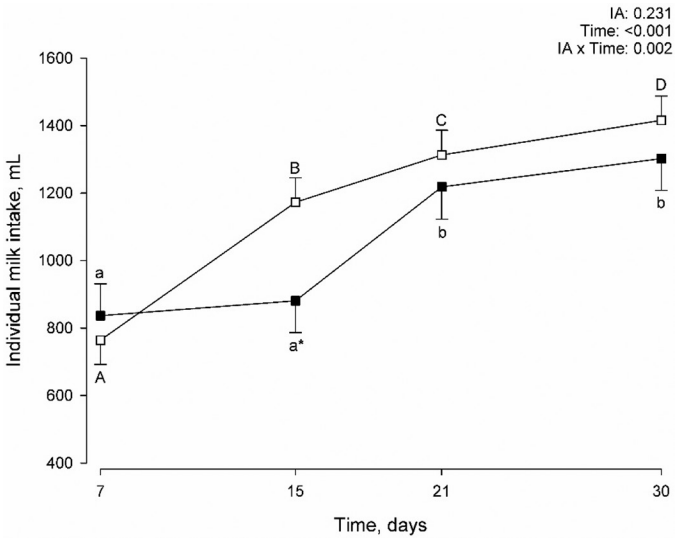

Figure 1. Individual milk intake (MI) in the LPS (■) and CON (□) groups throughout the experimental period (d 7, 15, 21, 30, relative to birth). Different lowercase letters (a, b) indicate significant differences ($P < 0.05$) in the MI recorded in the LPS group. Different uppercase letters (A–D) indicate significant differences ($P < 0.05$) in the MI recorded in the CON group. Significant differences between both groups are represented with (*). IA = intramammary administration. Data are expressed as LSM ± SEM.

DISCUSSION

Several strategies have been investigated to improve the performance and health of calves, lambs, and goat kids. Most of these studies have focused on enhancing colostrum and milk quality through nutritional management during gestation (Banchero et al., 2006; Celi et al., 2008; Gallo et al., 2020). However, the enrichment of colostrum and milk after parturition has also been tested. For instance, the inclusion of different molecules, such as antibiotics (Yousif et al., 2018), hormones (Sanei et al., 2012), algae (Samarasinghe et al., 2021) and minerals (Kamada et al., 2007; Pourliotis et al., 2012), in colostrum and milk has reduced the incidence of diarrhea and enhanced the immune system development in calves. Despite this, the effect of colostrum obtained from an intramammary challenge with LPS on goat kid immune status, serum metabolites, and performance have not been described before.

Udder inflammation triggers changes in the synthesis of components and alters the transfer of blood-derived molecules through the BMB (Bruckmaier and Wellnitz, 2017; Alcindo et al., 2022). As described by González-Cabrera et al. (2024), goats treated with an IA of LPS at parturition produced colostrum with higher IgG and IgM concentrations than those that received an IA without LPS. Similarly, Wellnitz et al. (2013) found that the IA of LPS to dairy cows can increase IgG_2 concentrations in milk (32 ± 8 and 173 ± 58 µg/mL at 0 and 6 h after challenge, respectively). Currently, it is not feasible to determine the concentration of IgG subclasses (i.e., IgG_1 and IgG_2) in goat colostrum, milk, or blood, as no quantitative methods are available. However, it is expected that the higher IgG concentration in colostrum from goats challenged with the IA of LPS was likely caused by an increased diffusion of IgG_2 through the leaky BMB or by a greater local synthesis and transfer of IgG_1 through transcytosis as reviewed by Hernández-Castellano et al. (2018) and Baumrucker et al. (2021). Although the present results showed no effects of the IA on plasma immunoglobulin concentrations, it would be expected that goat

Table 1. Plasma immunoglobulins (IgG and IgM) and serum metabolite concentrations, as well as rectal temperature (RT), BW, and individual milk intake (MI) on goat kids from the LPS (n = 15) and CON groups (n = 21)[1]

	Group[2]			Fixed effects		
Variable	LPS	CON	SEM	IA	T	IA × T
RT, °C	39.1	39.2	0.05	0.555	<0.001	0.348
BW, kg	4.9	4.5	0.28	0.172	<0.001	0.187
MI, mL	1,059.6	1,166.4	80.20	0.231	<0.001	0.002
IgG, mg/mL	14.2	11.3	1.55	0.096	<0.001	0.977
IgM, µg/mL	545.6 (330.8–899.9)	477.4 (295.3–771.7)		0.300	<0.001	0.409
Glucose, mg/dL	77.2	80.1	4.32	0.860	<0.001	0.206
Calcium, mg/dL	12.6	12.3	0.30	0.285	0.232	0.269
LDH, U/L	526.9	600.1	64.58	0.075	<0.001	0.824
TP, g/dL	5.1	4.8	0.18	0.099	<0.001	0.758
Albumin, g/dL	2.2	2.2	0.07	0.262	<0.001	0.549
Urea, mg/dL	12.1	12.3	1.04	0.844	<0.001	<0.001

[1]LPS = goat kids from dams that received an IA with LPS (50 µL of LPS in 2 mL of saline in each half udder); CON = goat kids from dams that received an IA without LPS (2 mL of saline in each half udder); IA = intramammary administration; LDH = lactate dehydrogenase; T = time; TP = total protein.

[2]Numbers in parentheses indicate minimum and maximum values.

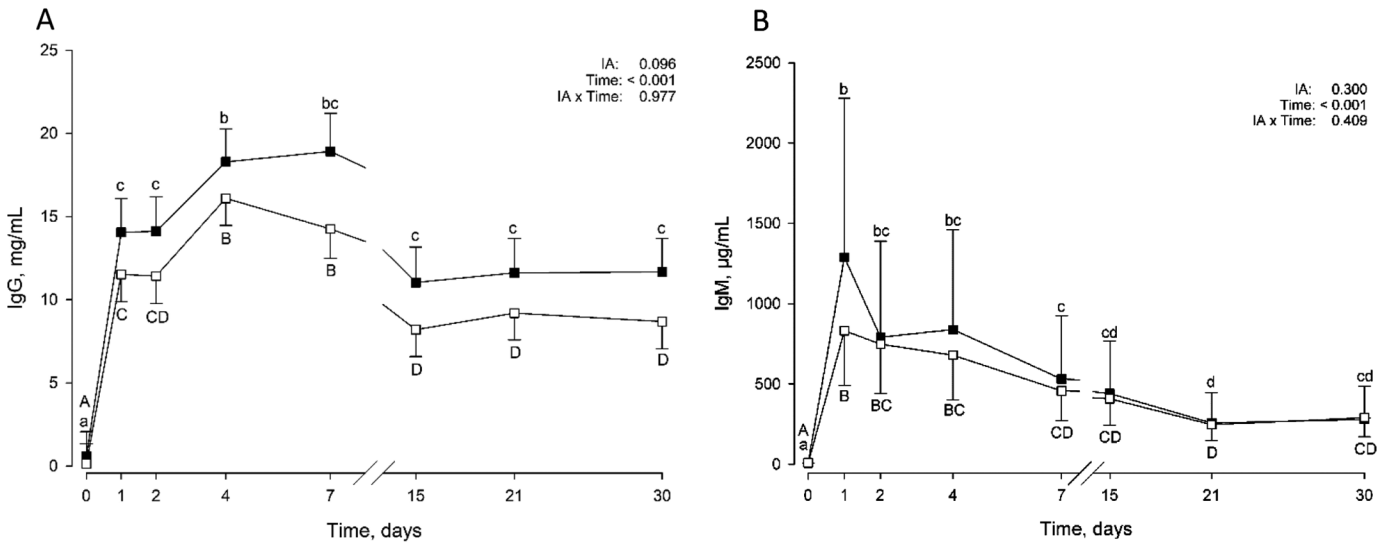

Figure 2. Plasma IgG (A) and IgM (B) in the LPS (■) and CON (□) groups throughout the experimental period (d 0, 1, 2, 4, 7, 15, 21, 30, relative to birth). Different lowercase letters (a–d) indicate significant differences ($P < 0.05$) in the LPS group. Different uppercase letters (A–D) indicate significant differences ($P < 0.05$) in the CON group. IA = intramammary administration. Data in panel A are expressed as LSM ± SEM. Data in panel B are expressed as mean (minimum and maximum).

kids receiving more immunoglobulin in colostrum would have higher IgG concentration in blood. This was previously described by Rodríguez et al. (2009), who assessed the effect of feeding newborn goat kids with colostrum containing different immunoglobulin concentrations, finding that circulating IgG and IgM levels were higher in those animals receiving colostrum with the highest IgG and IgM concentrations (i.e., 80 mg/mL and 7.4 mg/mL, respectively). However, despite some authors suggesting the existence of an uptake selectivity among intestine segments, no receptors have been associated with the intestinal absorption of immunoglobulins (Staley and Bush, 1985; Ontsouka et al., 2016). This nonspecific endocytosis of macromolecules might depend on the binding surface of the enterocyte membrane that can be saturated once exposed to colostrum. This could result in a limited capacity of absorption that might also explain the lack of differences in plasma IgG concentrations observed in this study. In addition, colostrum intake is essential to achieve a correct transfer of passive immunity (**TPI**), and its consumption should take place within the first hours of life (Argüello et al., 2004b), as enterocytes quickly lose the ability to absorb macromolecules in their native form (Stott et al., 1979; Moretti et al., 2013). Despite the 3-h delay in colostrum feeding, plasma IgG concentrations in goat kids were still above 10 mg/mL, meaning there was no failure of TPI and agreeing with previous studies in which animals were fed colostrum immediately after birth (Argüello et al., 2004b; Rodríguez et al., 2009). In addition, litter size and goat kid sex did not influence plasma immunoglobulin concentration in the present study, as reported by previous literature in dairy goats (Argüello et al., 2004b, 2006).

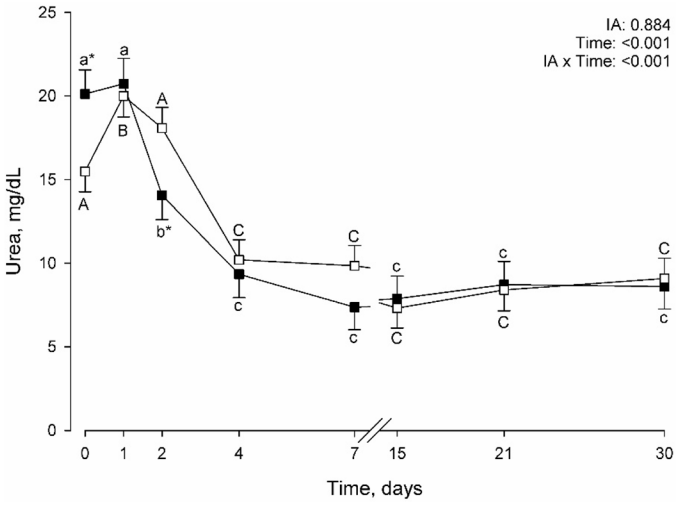

Figure 3. Urea concentration in the LPS (■) and CON (□) groups throughout the experimental period (d 0, 1, 2, 4, 7, 15, 21, 30, relatives to birth). Different lowercase letters (a–c) indicate significant differences ($P < 0.05$) in the LPS group. Different uppercase letters (A–C) indicate significant differences ($P < 0.05$) in the CON group. Significant differences between both groups are represented with (*). IA = intramammary administration. Data are expressed as LSM ± SEM.

Despite the reduced MI recorded in goat kids from the LPS group on d 15, no differences on goat kid BW were observed throughout the experimental period. Both groups grew evenly and constantly, which indicates that the lower MI did not affect growth in the LPS group.

These changes on MI could be associated with different individual consumptions patterns during the lactation period. Previous studies have demonstrated that animals under feed restriction can develop a compensatory gain weight once the normal intake is reestablished (Alves Costa et al., 2019; Hornick et al., 2000). Therefore, it is likely that either the reduction of MI could not be enough to induce growth changes in goat kids from both groups or that the LPS group could experience a compensatory growth resulting in no differences on BW between both groups.

Although goat kid performance was not affected in this study, it has been demonstrated that feeding milk from cows suffering mastitis can increase the incidence of diarrhea in calves (Abb-Schwedler et al., 2014). This is probably associated with the oral acquisition of bacteria responsible for inducing inflammation and ultimately diarrhea. In the present study, the IA of LPS was performed aseptically and goat kids from the LPS group did not show diarrhea neither after colostrum consumption nor during the rest of the experimental period. The present findings suggest that colostrum obtained from goats that have been intramammary challenged with LPS has no detrimental effects on goat kid health. This might be explained by the low LPS concentration in colostrum, as only 100 μg of LPS were infused in the udder (i.e., 50 μg of LPS diluted in saline solution, 2 mL, in each half) and only a colostrum volume equivalent to 10% of birth BW was fed to each goat kid. This is supported by Samarasinghe et al. (2020) who observed no diarrhea or inflammatory reactions in dairy calves that were fed milk with greater amounts of LPS (i.e., 12 μg/kg BW) on d 34 of life. The effect of LPS on gastrointestinal health has been well described in adult and newborn ruminants (Dong et al., 2011; Araujo et al., 2015). Once the LPS is synthesized, it can translocate from the gut lumen to circulation and induce a systemic and local inflammation leading to a disruption of the intestinal barrier known as "open" or "leaky" gut (Sullivan et al., 2023). This higher intestinal permeability has been associated with periods of stress, high-starch diets, or feed restriction in dairy cows (Kvidera et al., 2017; Fontoura et al., 2022). Yet, no studies have addressed the effects of oral LPS on gut permeability in newborn ruminants. Despite the assessment of oral LPS on goat kid health was not the aim of the present study, the lack of health issues could be likely associated with the action of salivary and gastric amylases as well as pancreatic lipases that may degrade the LPS before reaching the hind gut (Sissons, 1981).

In addition to performance variables, calcium, glucose, LDH, total protein, and albumin concentrations in serum did not differ between groups, agreeing with Alcindo et al., (2016) who also found no changes on serum total protein in albumin, immunoglobulins, and acute phase proteins (i.e., haptoglobin or transferrin) concentrations in goat kids that received colostrum from dams with subclinical mastitis. Despite previous studies have shown that milk chemical composition can be modified during udder inflammation (Hussain et al., 2012; Nogalska et al., 2020), changes in natural or experimentally induced mastitis may not be able to sufficiently affect colostrum composition and consequently lead to metabolic disruption and impairment of intestinal absorption of bioactive molecules. Although colostrum from the LPS group contained greater immunoglobulin concentrations, no effects in plasma immunoglobulins neither in serum albumin concentrations were observed, which can explain the lack of differences in total protein concentrations between both groups. In contrast, high urea concentrations were detected in the LPS group at birth. Increased levels of urea in blood can be associated with high protein diets and dehydration in cows, sheep, and goats (Giovanetti et al., 2019; Prahl et al., 2022). Indeed, the dam nutritional status during the last weeks of gestation might also influence the circulating urea concentration in the offspring. In this study all dams received the same diet and had free access to water prepartum. Therefore, these differences in circulating urea concentrations at birth cannot be associated with the nutritional status of the dams. In addition, high urea concentrations during the first 24 h of life have been associated with high rates of amino acid oxidation after colostrum consumption (Greenwood et al., 2002). However, the difference in urea concentration between groups were observed at birth, thus there is no physiological explanation to justify these findings.

CONCLUSIONS

The present study demonstrated that feeding colostrum from goats challenged with an IA of LPS at parturition, containing higher IgG and IgM concentration, did not affect performance, the TPI and serum metabolites in newborn goat kids. Nevertheless, future studies need to address the effects of mastitis on colostrum composition and its consequences on metabolism and gastrointestinal absorption of bioactive components in neonates.

NOTES

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Nonstandard abbreviations used: BMB = blood-milk barrier; CON = control; IA = intramammary administration; LDH = lactate dehydrogenase; MI = milk intake; RT = rectal temperature; T = time; TPI = transfer of passive immunity; TP = total protein.

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Capítulo 7

Chapter 7

Efectos del dolor en la expresión facial de cabritos lactantes

Effects of pain on the facial expressions of goat kids

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RESUMEN

La aparición de enfermedades en los cabritos lactantes tiene un fuerte impacto en su salud y condiciona su rendimiento en la vida adulta. Estos problemas suelen aparecer cuando la inmunidad adquirida a través de la ingesta de calostro ha sido insuficiente o por una disminución fisiológica de ésta a partir de los 15 días de vida (Argüello et al. 2004). Las escalas Grimace se han utilizado desde hace más de dos décadas para evaluar la expresión de emociones en pacientes no verbales (Hicks et al. 2001) y desde 2010 se validó su uso para determinar el dolor en ratones usados en experimentación (Langford et al. 2010). Ante la creciente preocupación por el bienestar en los animales de producción, el presente estudio pretende desarrollar una técnica novedosa no-invasiva para evaluar el efecto del dolor o malestar en la expresión facial de cabritos antes del destete. Para ello se usaron 60 cabritos (30 machos y 30 hembras) entre 1 y 20 días de vida procedentes de tres explotaciones ganaderas lecheras de tipo intensivo en la isla de Gran Canaria. Dado que la evaluación del dolor se realizó en base a la presencia de enfermedad (secreción nasal y dificultad respiratoria debida a neumonía, artritis o diarrea), un veterinario experimentado clasificó el dolor de los animales basándose en su experiencia, en una escala del 0 al 2, y se tomaron dos fotografías (frontal y lateral) del rostro de cada animal. En las imágenes se registraron la altura y ancho de la fisura palpebral, el ángulo de la boca lateralmente, y el ángulo de la nariz frontal y lateralmente. Los resultados del presente estudio demuestran que un nivel alto de dolor (nivel 2) incrementa la altura (0,83 y 1,29 cm, nivel de dolor 0 y 2 respectivamente) y el ancho de la fisura palpebral (1,85 y 2,35 cm, nivel de dolor 0 y 2 respectivamente) indicando que los cabritos con un nivel de dolor 2 no muestran un estrechamiento del área orbital al contrario de lo que ocurre en roedores y lagomorfos. Asimismo, el ángulo de la boca fue mayor en el nivel de dolor 2 que en el nivel 1 (41,0 y 37,5° nivel de dolor 2 y 1 respectivamente), mientras que el ángulo frontal de la nariz disminuyó en el nivel de dolor 2 con respecto a la ausencia de dolor (85,0 y 93,5°, nivel de dolor 2 y 0 respectivamente). En conclusión, este estudio constituye un enfoque novedoso en el desarrollo de una herramienta útil y práctica para determinar el dolor y malestar en cabritos antes del destete. Sin embargo, las variaciones en la conformación de la cabeza y la cara, así como el origen del estímulo doloroso (dolor térmico, mecánico o derivado

de una enfermedad) todavía deben ser evaluados en profundidad para evitar posibles sesgos en la clasificación.

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Effects of pain on the facial expressions of goat kids

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ABSTRACT

Pain assessment is essential in laboratory and farm animals. Grimace scales have been used for this purpose since 2010. The aim of the present study was to investigate how pain (due to disease presence) affects the main facial expressions of goat kids. For this purpose, 60 goat kids aged 1 to 20 days were included in the study. An experienced veterinarian graded the animals' pain based on his experience (pain 0, 1, and 2), and two photographs (frontal and lateral) were taken. The following measurements were recorded: Height and width of the palpebral fissure, mouth angle, angles of the nose in profile and front. Pain level affected the height (0.83 and 1.29 cm, pain level 0 and 2 respectively, $p < 0.001$) and width of the palpebral fissure (1.85 and 2.35 cm, pain level 0 and 2 respectively, $p < 0.001$), which increased at pain level 2. Thus, narrowing of the eye was not observed when pain level increased. The angle of the mouth increased at pain level 2 (39.2 and 41.0 degrees, pain level 0 and 2 respectively, $p = 0.013$), and the frontal angle of the nose decreased at pain level 2 (93.5 and 85.0 degrees, pain level 0 and 2 respectively, $p = 0.009$).

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Pain evaluation; goat kids; grimace; facial

Introduction

Pain assessment in animals is a relevant topic for researchers, animal scientists and veterinarians in a daily basic frequency. European Directive 2010/63/EU is very clear regarding the assessment of pain in scientific procedures involving animals. It requires procedures to be classified as 'non-recovery', 'mild', 'moderate', and 'severe'. United States Department of Agriculture also establishes a classification of pain level into four categories (B, C, D and E, Animal Welfare Act 2024). Pain assessment is critical on farms because there is a direct correlation between pain, stress, and poor performance (Chulayo and Muchenje 2015). Veterinarians need to assess animal pain in order to prescribe treatment and evaluate the progress of recovery.

The 3Rs (Replacement, Reduction, Refinement) concept proposed by Russell and Burch (1959) includes pain assessment as a key factor to improve refinement. The use of grimace scales was initially developed to humans, where emotions are reflected in facial expressions. This scale is useful for nonverbal human patients (Hicks et al. 2001). The pain-face relationship was first used by Langford et al. (2010) to assess pain in mice. These authors correlated orbital constriction, nasal bulge, cheek bulge, ear position, and whisker changes with the degree of pain.

After 2010, grimace scales were developed for other laboratory animals such as rats and rabbits. More recently, grimace scales have been developed for farm animals such as ewes (McLennan et al. 2016; Hager et al. 2017), lambs (Guesgen et al. 2016), cattle (Muller et al. 2019), pigs (Vullo et al. 2020), or piglets (Viscardi et al. 2017), but little information is available for goats or their kids.

Regarding goats, Lou (2020) conducted a study on the application of the grimace scale in goat kids during disbudding. The study concluded that the grimace scale is a valid and reliable tool for assessing acute pain in goat kids undergoing disbudding. Additionally, the research found that the use of local anesthesia can significantly reduce the pain associated with the procedure.

In a more recent study, Weeder et al. (2023) described an experiment aimed at determining the optimal dose of amphotericin B to induce transient lameness in meat goats for research purposes. The authors developed a facial grimace scale for goats to evaluate their pain responses. According to the paper, the optimal dose of amphotericin B was found to be 5 mg/0.25 mL, resulting in the most severe and consistent lameness among the goats. The study also introduced a goat grimace scale based on five facial features that can be utilized to assess pain in goats (ear position, nostril shape and dilation, orbital tightening, and cheek tightening).

Recently, Hussein and Al-Nakshabendy (2023) explored the use of facial expressions and infrared thermography to measure positive emotions in goats. The authors stroked the goats' bodies in three areas (forehead, neck, and withers) and observed their facial grimace scale, ear postures, and surface temperatures. The study revealed that stroking induced

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significant changes in most facial units, ear positions, and eye and nasal temperatures, indicating a positive emotional valence in goats. The paper concludes that facial expressions and peripheral temperatures are vital indicators of positive emotions in goats.

Due to a prevailing lack of knowledge regarding the utilization of facial expressions as pain indicators at the farm level, the primary objective of the present study was to comprehensively evaluate the impact of pain on the facial expressions of goat kids without inducing any deliberate pain stimuli under farm conditions. In light of the limited understanding in this area, the study sought to bridge the gap by examining how pain manifests in the natural environment of the farm setting and assessing the corresponding facial expressions exhibited by goat kids under these conditions. The investigation aimed to contribute valuable insights into the recognition and interpretation of facial expressions as potential indicators of pain in goat kids without the influence of deliberate pain induction procedures.

Material and methods

Ethical issues

All procedures incorporated into the current study fall outside the scope of Directive 2010/63/EU due to the specific definition of a procedure outlined in the directive. According to the directive, a 'procedure' encompasses any use, whether invasive or non-invasive, of an animal for experimental, scientific, or educational purposes, with known or unknown outcomes. Moreover, it includes activities that may cause the animal a level of pain, suffering, distress, or lasting harm equivalent to, or greater than, that caused by the introduction of a needle in accordance with good veterinary practice.

In the context of our study, it is crucial to emphasize that the procedures undertaken did not induce pain in the animals. The only stress experienced by the animals was associated with the gentle handling required during the experimental protocols. This distinction is paramount in ensuring compliance with ethical standards and animal welfare guidelines. By explicitly highlighting that the procedures did not cause pain but only mild stress associated with gentle handling, we underscore the ethical and humane nature of our approach. This clarification further solidifies the ethical foundation of the study, aligning with the principles of minimizing harm and ensuring the welfare of the animals involved.

Animals and study location

In this research endeavour, a total of sixty Majorera goat kids, comprising 30 males and 30 females, were deliberately chosen for the study. These animals, artificially reared to ensure controlled conditions, spanned an age range of 1 to 20 days, a critical period in their early developmental stages. The meticulous selection of subjects was conducted from a diverse pool, originating from three distinct livestock farms situated in southeastern Gran Canaria, Canary Islands, Spain. The geographical coordinates of the study locations are recorded as 27.8724N latitude and −15.5012W longitude, providing a precise reference point for the study's contextualization within the specific environmental conditions of this region. The intentional inclusion of both genders and the age diversity within the cohort aim to capture a comprehensive snapshot of developmental nuances and potential gender-specific variations in the parameters under investigation. This meticulous approach to subject selection and detailed geographical specification ensures the robustness and generalizability of the findings within the specific context of the Majorera goat population in southeastern Gran Canaria.

Disease evaluation

An experienced veterinarian classified the animals into three categories (adapting the classification from Zentrich et al. 2023) of pain based on their clinical signs: Pain 0 – no pain (no evidence of disease), Pain 1 – moderate pain (some signs of disease but able to stand), and Pain 2 – severe pain (severe signs of disease and difficulty standing) (see Table 1). The most frequent signs were nasal discharge and respiratory distress due to pneumonia, lameness, joint swelling, and perianal fecal contamination from diarrhea.

Imagen capture and facial action quantification

In the course of this study, the animals were gently restrained for a brief duration, during which two photographs were captured utilizing a digital camera, specifically the Nikon D3100 (Tokyo, Japan). The photographic documentation was executed at a standardized distance of 60 cm from each animal, ensuring consistency in image acquisition. Notably, two images were captured for each subject – a frontal view and a profile view from the right side.

The photographic sessions transpired within the confines of the farm's yards. This strategic decision was made to minimize stress on the animals, as relocating them to an alternative location could potentially induce distress. By conducting the photographic documentation within familiar surroundings, we aimed to maintain a stable and comfortable environment for the subjects, thereby safeguarding the integrity of the collected data.

Table 1. Clinical score.

Parameter	Clinical signs	Score
Vocalization	None	0
	Slightly muffled voices	1
	Muffled voices	2
Activity	Sleeping and resting	0
	Frequent change of position	1
	Restless, directionless walking	2
Food/water or milk intake	Normal,	0
	Reduced	1
	Inappetence	2
General appearance	Sniffing and looking for straw, hay, or wáter,	0
	playing with neighbourns	1
	Downcast, turning head to side	2
	Apathetic	
Pain	No evidence of disease	0
	Innespessific clinical signs but able to stand	1
	Severe signs of disease: pneumonia (discharge and respiratory distress), lameness, joint swelling or perianal fecal contamination from diarrhea	2

Adapted from Zentrich et al. (2023).

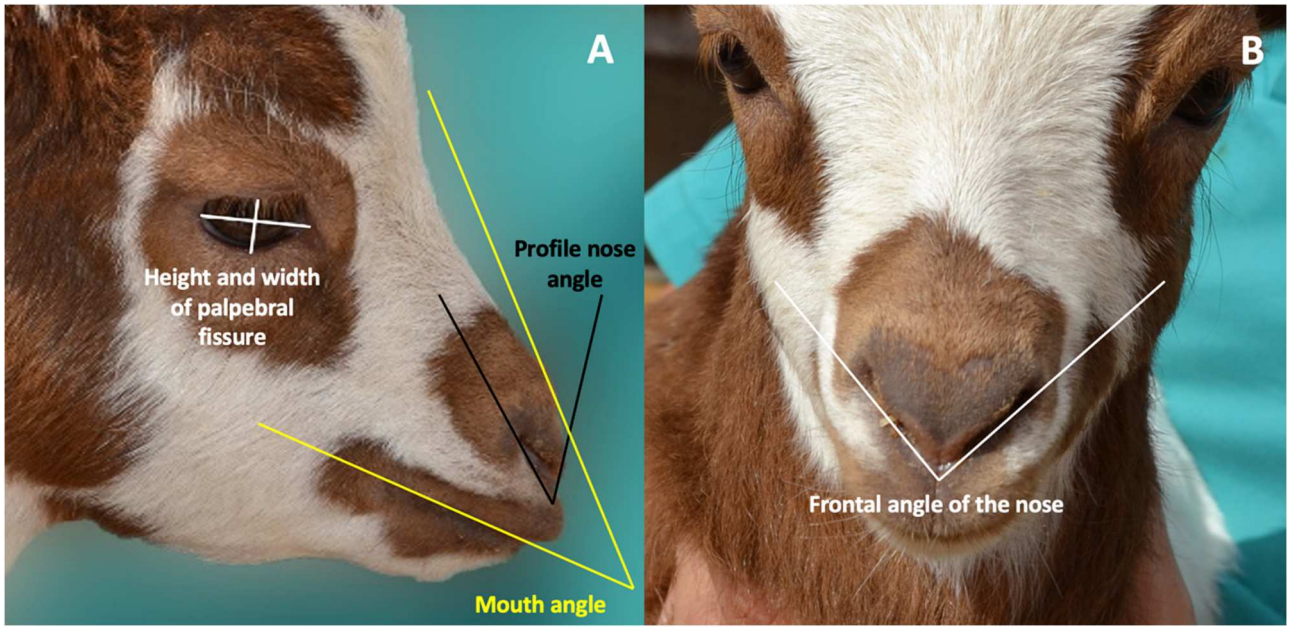

Figure 1. Determination of height and width of palpebral fissure, angle of the mouth, and frontal and in profile angles of the nose. A, height of palpebral fissure, straight line from the centre of the lower eyelid to the centre of the upper eyelid, intersecting the midpoint of the pupil. Width of palpebral fissure, straight line from the lateral to the medial corner of the right eye, crossing the middle of the pupil. Profile nose angle, one axis was placed over the right nostril, and the other axis was aligned to touch the most rostral point of the nose. The connecting vertex was then situated at the most ventral point of the nose. Mouth angle, one axis parallel to the oral commissure, while the other axis was drawn sagittally from the frontal bone at the level of the supraorbital foramina, tangentially touching the tip of the nose. The connecting vertex was positioned in front of the upper lip. B, frontal angle of the nose, two axes were strategically positioned over each nostril, with the connecting vertex situated at the convergence point of the nostrils.

In the current investigation, our focus centered on the quantification of three distinct facial expressions: eye opening, nose angles, and mouth angle. To precisely assess these expressions, a total of five measurements were undertaken, targeting specific features such as the height and width of the palpebral fissure, the angle of the mouth, and the angles of the nose in both profile and frontal views (refer to Figure 1).

For the measurements of the palpebral fissure, Adobe Photoshop (Adobe Systems Incorporated, U.S.A., V. CS4, 11.0) was employed to determine both the height and width. The height measurement involved drawing a straight line from the centre of the lower eyelid to the centre of the upper eyelid, intersecting the midpoint of the pupil. Meanwhile, the width measurement was conducted by drawing a straight line from the lateral to the medial corner of the right eye, crossing the middle of the pupil (see Figure 1).

To measure the frontal angle of the nose, two axes (represented by yellow and blue squares in Figure 1) were strategically positioned over each nostril, with the connecting vertex (depicted by the red square) situated at the convergence point of the nostrils. In the profile picture, one axis (yellow square) was placed over the right nostril, and the other axis (blue square) was aligned to touch the most rostral point of the nose. The connecting vertex (red square) was then situated at the most ventral point of the nose.

The measurement of the mouth angle involved the placement of one axis parallel to the oral commissure, while the other axis was drawn sagittally from the frontal bone at the level of the supraorbital foramina (blue square in Figure 1), tangentially touching the tip of the nose. The connecting vertex (red square) was positioned in front of the upper lip to ensure accurate measurement and representation of the mouth angle. These measurements were facilitated using the online software RULER, a tool developed by the Polytechnic University of Valencia, Spain (available at https://www.ergonautas.upv.es/herramientas/ruler/ruler.php).

Statistical analysis

Analysis was performed using RStudio version 1.1 (RStudio Inc, Massachusetts, U.S.A.). Statistical significance was set at $P \leq 0.05$. Normality was checked using the Shapiro–Wilk test. The height and width of palpebral fissure, mouth angles, and profile angle of the nose were normally distributed ($P = 0.145$, 0.078, 0.559, and 0.258, respectively). The frontal angle of the nose was not normally distributed ($P = 0.001$).

The effect of pain level on height and width of palpebral fissure, mouth angle, and profile nose angle was assessed using the one-way ANOVA. Differences between means were tested using the Tukey HSD test. The effect of pain level on the frontal angle of the nose was evaluated using the Kruskal–Wallis test. Differences between mean values were tested using pairwise comparison with the Wilcoxon rank sum test.

Results and discussion

Tables 2 and 3 present comprehensive descriptive statistics delineating the observed measurements based on their adherence to either normal or non-normal distribution patterns. Notably, in the context of livestock species research (Guesgen

Table 2. Descriptive statistics of frontal angle of the nose in degrees.

	Minimum	1st Quartile	Median	3rd Quartile	Maximum
Frontal angle of the nose	49.00	83.75	89.00	94.25	102.00

Table 3. Descriptive statistics for height and width of palpebral fissure, angle of the mouth and in profile angle of the nose.

	Minimum	Mean	Standard deviation	Maximum
Height of palpebral fissure (cm)	0.62	1.09	0.30	1.83
Width of palpebral fissure (cm)	1.37	2.13	0.41	3.53
Angle of the mouth (degrees)	31.00	39.15	4.12	50.00
Angle of the nose in profile (degrees)	26.00	48.48	10.99	80.00

et al. 2016; Viscardi et al. 2017), the predominant methodology has involved the application of grimace classification, as established in mouse pain assessment models (Langford et al. 2010). In this paradigm, expressions of pain are categorized into degrees – ranging from absent to moderate to severe – rather than being quantified in conventional units such as centimetres or angular degrees.

Regrettably, this divergence in the approach to pain measurement has rendered cross-study comparisons challenging. The absence of a standardized metric, such as a common unit of measurement, hinders the juxtaposition of findings across various manuscripts. Consequently, this methodological incongruity precludes a meaningful comparison with the broader body of literature in the field.

The Table 2 shows the minimum, 1st quartile, median, 3rd quartile and maximun for the Frontal angle of the nose (49, 83.75, 89, 94.25 and 102 degree, respectively).

Significant variations in pain levels were discerned in the dimensions of the palpebral fissure, mouth, and frontal nasal angles among goat kids, as illustrated in Tables 4 and 5. The phenomenon of eye narrowing, a hallmark feature across various Grimace scales (Guesgen et al. 2016; Viscardi et al. 2017; Lou 2020; Weeder et al. 2023), is consistently described. Eye narrowing is characterized by tension in the ocular region, leading to a reduction in palpebral fissure width and eventual eye closure.

Contrary to findings in mice (Langford et al. 2010), rats (Sotocinal et al. 2011), seals (MacRae et al. 2018), and even goats (Lou 2020; Weeder et al. 2023), Table 4 unveil a noteworthy divergence. With an escalation in pain levels from 0 to 2 (Table 4), there was a significant increase in both palpebral fissure height and width. This contrasts with the observed eye closure in other species under similar circumstances. The apparent controversy in these outcomes could be attributed to two primary factors. First, there is the proposition, as posited by Mogil et al. (2020), that species exhibit differential grimacing responses to acute noxious stimuli. Second, the temporal aspect of grimacing is crucial, with chemical/inflammatory or postsurgical procedures reported to manifest over varying timeframes – ranging from minutes to hours or even after 24 h following the stimuli (Mogil et al. 2020).

Table 4. Least square means of mouth angle and side nose angle according to pain classification.

Measures	Pain 0	Pain 1	Pain 2	SD	*P*
Height of palpebral fissure (cm)	0.83^{a}	1.15^{b}	1.29^{b}	0.30	0.001
Width of palpebral fissure (cm)	1.85^{a}	2.19^{b}	2.35^{b}	0.41	0.001
Angle of the mouth (degrees)	39.20^{ab}	37.25^{a}	41.00^{b}	4.12	0.013
Angle of the nose in profile (degrees)	52.50	46.80	46.15	10.99	0.133

SD, standard deviation. Different letters in the same row means least squares means statistical differences according *P* value.

Table 5. Kruskal–Wallis analysis and post hoc Wilcoxon rank for Frontal angle of the nose.

	Pain 0	Pain 1	Pain 2	*P*
Frontal angle of the nose (degrees)	93.50^{a}	87.00^{ab}	85.00^{b}	0.009

Different letters in the same row means statistical differences according *P* value.

It is pertinent to note that the magnitude of pain in our study was contingent upon farm-related illnesses, and the temporal dynamics of grimacing were not explicitly controlled. Nonetheless, this approach aligns with a pragmatic perspective, aimed at providing veterinarians with a genuine and applicable tool for on-farm pain assessment.

The angle of the mouth (Table 4) was significantly higher in pain level 2 than in pain level 1, but both (pain levels 1 and 2) showed no differences from pain level 0. The mouth angle is not present in the grimace scales of mice (Langford et al. 2010) or rats (Sotocinal et al. 2011), but was used by (Guesgen et al. 2016) in lambs. The latter authors described that lambs in pain show a flatter lip line than lambs not in pain, and that are consistent with what is indicated in Table 4 for mouth angle. It is important to note that the increase in the angle of the mouth is small and likely difficult for veterinarians or goat farmers to observe on the farm.

The level of pain significantly decreased the frontal angle of the nose ($P = 0.009$). Pain level 2 was significantly different from pain level 0. Similar results were observed by (Guesgen et al. 2016) who described the reduction in the frontal angle of the nose as a pointed nose.

The grimace scales of sheep, mice, rats, rabbits, and horses show similarities that support the idea that emotions are associated with similar facial expressions in all mammalian species, as suggested by Williams (2002) and Dalla Costa et al. (2014). However, it is important to note that the same individuals were involved in the creation of all grimace scales, which may have resulted in some overlap due to their prior knowledge of changes in facial features. Furthermore, the differences in facial expressions between the grimace scales could be due to variations in facial size, composition, and musculature between goat kids, lambs, mice, rats, and rabbits. In addition, it is possible that different types of pain (e.g. disease-related, thermal, chemical, or mechanical pain) elicit slightly different facial expressions, although this requires further investigation.

Conclusion

The present study has shown that the facial expressions of goat kids change as a function of pain intensity on farm condition.

The question is whether these changes in facial expression can be easily detected by veterinarians or goat keepers. Another limitation of the present study was the persistence of grimacing after noxious stimuli triggered by the pathological process. However, the strategy of measuring facial expressions opens a new way to evaluate pain in farm animals.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Discusión general

General discussion

DISCUSIÓN GENERAL

Los estudios planteados en la presente Tesis Doctoral se integran en un proyecto de investigación que tienen como objetivo general mejorar la calidad del calostro, la inmunidad adquirida, el desarrollo y el bienestar en los cabritos neonatos.

Los resultados obtenidos en el Capítulo 4 indican que alimentar a las cabras lecheras con un alto contenido de almidón durante el último mes de gestación influye en la calostrogénesis, aumentando la concentración de IgG en el calostro. De forma similar, el Capítulo 5 demuestra que la administración vía intramamaria de lipopolisacáridos en el momento del parto es capaz de aumentar la concentración de inmunoglobulinas (IgG e IgM) en el calostro. Si bien el incremento de inmunoglobulinas observado en el Capítulo 5 puede atribuirse a un aumento de la permeabilidad de la barrera sangre-leche (Wall et al., 2015; Wellnitz y Bruckmaier, 2021), aún se desconoce qué mecanismos desencadenan este incremento cuando este se debe a modificaciones nutricionales. Se podría pensar que la suplementación energética induce cambios en el sistema neuroendocrino, modulando el metabolismo y la función celular, produciendo cambios en la expresión génica y factores de transcripción responsables de la síntesis y transferencia de componentes inmunes en la glándula mamaria. A pesar de que la literatura apoya esta hipótesis (Groner, 2002; Van Harten et al., 2013; Fougère and Bernard, 2019), el conocimiento sobre la calostrogénesis es todavía insuficiente y requiere más investigación. Por otro lado, la ausencia de diferencias en la concentración plasmática de IgG en las cabras de ambos ensayos también supone cierta controversia. Por lo tanto, se puede hipotetizar que la IgG presente en el calostro no procede en su totalidad de la circulación sanguínea, sino que existen otras fuentes de IgG que contribuyen a su concentración final en el calostro y, que los mecanismos de transcitosis y reciclaje de la IgG pueden ser responsables de restablecer constantemente los niveles plasmáticos de IgG (Baumrucker et al., 2021). Además, también es posible que esta transferencia de IgG desde la sangre a la glándula mamaria tenga lugar de forma progresiva y que, por tanto, la frecuencia y técnicas de muestreo en los diferentes ensayos deban ser revisadas de cara a reflejar las posibles fluctuaciones de IgG en sangre.

De acuerdo con la literatura disponible, cabría esperar que un aumento en el contenido de almidón en la dieta durante el último mes de gestación aumentase la disponibilidad de glucosa como sustrato para la síntesis de lactosa, y esto, a su vez, desencadenara un incremento de la producción y/o una modificación de la composición del calostro (Banchero et al., 2006). Sin embargo, y de acuerdo con los resultados de la presente Tesis Doctoral, esta ruta metabólica no parece estar influenciada por el aumento del contenido de precursores de la glucosa en la dieta como el almidón. De acuerdo con Hare et al. (2023), la utilización de glucosa en razas de alta producción lechera podría estar ya maximizada durante la fase de calostrogénesis, de modo que esto podría explicar la ausencia de respuesta a la suplementación energética. Además de la influencia inherente a la especie y raza, es importante resaltar que el tipo y fuente del nutriente seleccionado, así como la duración de la suplementación son factores determinantes en la respuesta. Por otro lado, algunos autores han observado una disminución transitoria de la producción de leche en vacas poco después de ser tratadas con LPS vía intramamaria (Silanikove et al., 2011; Opgenorth et al., 2024). Sin embargo, ningún estudio había demostrado antes los efectos de la administración intramamaria de LPS sobre la producción de calostro. El Capítulo 5 demuestra que el volumen de calostro producido no se ve influenciado por la respuesta inflamatoria desencadenada al administrar LPS. Probablemente, la administración de LPS en ubres llenas y al término de la calostrogénesis expliquen esta ausencia de efecto. No obstante, este hallazgo coincide con Salama et al. (2020) quienes no encontraron diferencias en la producción de leche en un período de 72 horas entre ubres vacías tratadas y no tratadas con LPS en cabras de raza Murciano-Granadina. Finalmente, para determinar un verdadero efecto sobre la producción y composición de calostro habría que evaluar el efecto del LPS durante un período de tiempo mayor y coincidente con la calostrogénesis. Los hallazgos obtenidos en ambos estudios podrían llevar a pensar que la glándula mamaria cuenta con unos mecanismos fisiológicos compensatorios que le permiten mantener una producción relativamente estable ante modificaciones en la disponibilidad de nutrientes y ante estímulos inflamatorios.

Otro de los hallazgos más relevantes de la presente Tesis Doctoral es que la mejora de la calidad del calostro (aumento de la concentración de IgG) no necesariamente determina

una mejor inmunidad en los cabritos (Capítulos 4 y 6). Cabría esperar que el aumento de la concentración de IgG en el calostro se viera reflejada también en la concentración plasmática de IgG en los cabritos. Sin embargo, los resultados parecen indicar que el consumo de un calostro de buena calidad (≥ 20mg/ml de IgG en caprino) independientemente de su concentración de IgG si ésta es superior al valor de referencia, es suficiente para garantizar una correcta transferencia de inmunidad pasiva sin ocasionar diferencias en las concentraciones plasmáticas. Esto coincide con Besser et al. (1985) quienes ya habían observado que los terneros podían tener una limitación fisiológica para la absorción de IgG. De acuerdo con Saldana et al. (2019), la eficacia aparente de absorción de IgG es mayor en aquellos terneros que reciben calostro de calidad media (65,7 ± 0,84 mg/ml; 38,1% de absorción aparente) en comparación con los alimentados con calostro de alta calidad (98,1 ± 0,84 mg/ml; 25% de absorción aparente). De este modo, las estrategias desarrolladas en la presente Tesis Doctoral podrían tener una aplicación en aquellos casos en los que se conozca o estime de antemano la necesidad de mejorar la calidad del calostro, como ocurriría por ejemplo en animales primíparos, en partos inducidos o en animales con baja productividad (Castro et al., 2011b; Romero et al., 2013; Zhou et al., 2023).

Por otro lado, se sabe que los animales de producción pueden estar expuestos a diversos estímulos dolorosos derivados de procesos rutinarios como son la castración, el descornado, el parto o el propio ocasionado por lesiones o enfermedades. Los animales de corta edad son especialmente susceptibles a desarrollar enfermedades debido a un mal manejo del encalostrado (volumen, calidad, consumo desde el nacimiento) o a un sistema inmunológico inmaduro. Además, la expresión del dolor y los signos de enfermedad en estos animales están frecuentemente enmascarados, por lo que este tipo de técnicas no invasivas y fácilmente accesibles en el entorno ganadero son claves para identificar, de forma precoz, los signos de dolor. Aunque el presente estudio muestra modificaciones en la expresión facial de cabritos con una enfermedad infecciosa, estos cambios no coinciden con los descritos previamente en roedores (Langford et al., 2010). La escasa literatura nos puede llevar a especular que estas diferencias se deben probablemente a factores inherentes a la especie (morfología facial) o a la naturaleza del estímulo doloroso (dolor térmico, mecánico o causado por

una enfermedad). De hecho, Guesgen et al. (2016) observaron un ángulo de la boca más estrecho y en una menor amplitud del área orbital antes y después del recorte de la cola en corderos. Esto parece confirmar que, tanto la especie como el tipo de estímulo doloroso juegan un papel clave en la expresión facial del dolor o malestar. El presente trabajo pretendía establecer unos criterios de valoración del dolor y malestar que podrían ser usados en el entorno científico y ganadero para estimar el impacto de una enfermedad y de prácticas de manejo o ensayos experimentales invasivos en el bienestar de estos animales. Si bien se tratan de resultados preliminares, la escala Grimace en cabritos lactantes parece ser una técnica que, junto a otros criterios de salud, puede ayudar a valorar el impacto de estímulos dolorosos y a determinar el mejor momento de aplicación de un tratamiento veterinario antes de que aparezcan signos más graves de enfermedad como la anorexia y la pérdida de peso.

GENERAL DISCUSSION

The studies performed for this PhD thesis are part of a research project aiming to improve colostrum quality, acquired immunity, development, and welfare in newborn goat kids.

The results obtained in Chapter 4 indicate that feeding dairy goats with a high-starch diet during the last month of gestation has an impact on colostrogenesis by increasing the concentration of IgG in colostrum. Similarly, Chapter 5 demonstrates that the intramammary administration of lipopolysaccharides (LPS) at parturition can increase the concentration of immunoglobulins (IgG and IgM) in colostrum. While the increased colostrum IgG and IgM concentrations observed in Chapter 5 can be attributed to a higher permeability of the BMB (Wall et al., 2015; Wellnitz and Bruckmaier, 2021), the mechanisms that trigger this increase due to dietary modifications are still unknown. It could be hypothesized that energy supplementation induces changes in the neuroendocrine system, modulating metabolism and cellular function, changing gene expression and transcription factors responsible for the synthesis and transfer of immune components to the mammary gland. Although the literature supports this hypothesis (Groner, 2002; Van Harten et al., 2013; Fougerè et al., 2019), some molecular mechanisms controlling colostrogenesis are still unknow. The lack of differences in plasma IgG concentrations in dams from both studies are also controversial. It can be hypothesized that the IgG present in colostrum does not entirely come from blood, but there are other sources of IgG that contribute to its concentration in colostrum. Thus, the mechanisms of transcytosis and recycling of IgG may be responsible for restoring circulating IgG concentrations in dams (Baumrucker et al., 2021). Furthermore, it is also possible that this transfer of IgG from blood to the mammary gland occurs progressively, and, therefore, the frequency and sampling techniques in the different studies should be revised to reflect those possible blood IgG fluctuations.

According to previous research, it could have been expected that the increase of dietary starch during the last month of gestation would increase blood glucose and its availability as a substrate for lactose synthesis, which in turn, it would increase colostrum production (Banchero et al., 2006). However, according to the present results, this metabolic pathway in dairy goats does not seem to be influenced by the dietary

content of glucose precursors such as starch. According to Hare et al. (2023), glucose partitioning to the mammary gland in high yielding breeds may already be maximized during colostrogenesis which could explain the lack of response to energy supplementation. Besides the inherent effect of species and breed, it is important to highlight that the type and source of nutrient, as well as the length of supplementation could also shape the response to the energy supplementation. In addition, some studies have observed a transient decrease of milk yield in cows after an intramammary administration of LPS (Silanikove et al., 2011; Opgenorth et al., 2024). This down regulation of milk production could be due to a rapid shift in cellular metabolic pathways, redirecting nutrients to support the immune system function. Chapter 5 demonstrated that colostrum yield is not influenced by the immune response triggered by the LPS administration. It can be speculated that the administration of LPS in full udders might dilute the LPS capacity to trigger an acute immune response, resulting in a lack of inflammation at the end of colostrogenesis. Thus, it can be expected that the exposure and interaction of the LPS with epithelial and immune cells would be increased if the same dose would have been administered in empty udders. Actually, Salama et al. (2020) found no differences in milk yield over a 72-hour period in empty half udders challenged with LPS, indicating that either LPS does not trigger nutrient partitioning to respond to the inflammatory stimulus or the LPS dose was not sufficient (i.e., 10 µg of LPS / 2mL saline) to trigger the expected effect. Besides, colostrum synthesis takes place over 3 to 4 weeks before parturition, the administration of LPS for an extended period of time before kidding might be a better approach to assess its effects on colostrum yield and composition. Findings from both studies indicate that the mammary gland might be able to develop a compensatory response to changes in nutrient availability or inflammation to maintain lactation.

Further, another evidence emerging from this PhD thesis is that the improvement of colostrum quality (i.e., higher IgG concentrations) does not necessarily determine a better TPI in newborn goat kids (Chapters 4 and 6). It could have been expected that increased colostrum IgG concentration would have caused increased plasma IgG concentrations in the goat kids. However, the results indicate that the intake of good quality colostrum (i.e., ≥ 20 mg/mL of IgG in goats), regardless of its IgG concentration

when its above the threshold, can be enough to ensure a correct TPI. This agrees with Besser et al. (1985) who reported that there is a physiological limitation for intestinal IgG absorption, as calves fed greater amounts of IgG did not showed higher absorption rates. In fact, Rodriguez et al. (2009) found that feeding colostrum with different IgG concentrations (i.e., 20, 40, 60, and 80 mg/mL) resulted in no differences on the immunity acquired by newborn goat kids. Supporting this evidence, Saldana et al. (2019) demonstrated that the apparent efficiency of IgG absorption is higher in calves fed medium quality colostrum (i.e., 65.7 ± 0.84 mg/mL; 38.1% apparent efficiency of absorption) compared to those receiving high quality colostrum (i.e., 98.1 ± 0.84 mg/mL; 25% apparent efficiency of absorption). Thus, it can be hypothesized that there might exist an uptake selectivity among intestine segments which can be saturated when exposed to high amounts of immunoglobulin (Staley and Bush, 1985; Ontsouka et al., 2016). Yet, no studies have demonstrated an active uptake of immunoglobulins mediated by specific receptors in newborn ruminants. Thus, both strategies developed in this PhD thesis could have a valuable application in those circumstances in which colostrum quality needs to be improved as it would occur in induced parturition, preterm kidding, primiparous animals or in animals exhibiting low colostrum yield or quality (Castro et al., 2011; Romero et al., 2013; Zhou et al., 2023).

Livestock animals are commonly exposed to management procedures such as castration or dehorning, or injuries and diseases. All of them cause several noxious stimuli which may stress the animals, which in turn increases the susceptibility to suffer infectious diseases and reduces animal performance. Young animals are especially vulnerable to infectious diseases due to poor colostrum management (i.e., low volume or quality, feeding timing, microbiological quality) and their immature immune system. In fact, inflammatory pain is often caused by the sensibilization of nociceptors by mediators (i.e., cytokines, lipids) which are synthesized by immune cells or even bacteria and their toxins (i.e., LPS; Baral et al., (2019). However, pain is frequently masked in ruminants, thus, the development of non-invasive and easily accessible on-farm techniques can be useful to detect early signs of pain and consequently, improve their health and welfare. Although the present study shows changes on the facial expression of pre-weaned goat kids experiencing an infectious disease, these changes do not completely agree with

those previously reported in rodents (Langford et al., 2010). It can be speculated that these differences are probably associated to species-specific factors (i.e., facial and ear morphology, presence or absence of whiskers) or the type of the noxious stimulus (i.e., neuropathic or inflammatory pain). Indeed, Guesgen et al. (2016) observed a narrower mouth angle and a greater orbital tightening before and after tail docking in lambs, indicating different facial expression even between lambs and goat kids. Although the present study constitutes a preliminary approach to pain assessment in pre-weaned goat kids, the Grimace scale seems to be a technique that, together with other health and behaviour criteria, can help the detection and classification of pain. This will provide a useful tool for producers, researchers and veterinarians to act before the onset of more severe signs of disease.

Fortalezas y limitaciones

Strengths and limitations

FORTALEZAS Y LIMITACIONES

El Capítulo 3 pone de manifiesto importantes lagunas de conocimiento relativas a la fisiología y la modulación de la calostrogénesis en el ganado caprino, recopilando los mecanismos fisiológicos complejos que intervienen en este proceso y evidenciando el impacto de algunas estrategias nutricionales, de la estimulación de la respuesta inmune local y del manejo del secado sobre la calostrogénesis en rumiantes. Sin embargo, la escasez de literatura en el ganado caprino supone, todavía, una gran limitación para la revisión, comparación e interpretación de resultados.

El Capítulo 4 constituye el primer estudio evaluando el efecto de un aumento de la cantidad de almidón en la dieta durante el último mes de gestación en el ganado caprino, sobre la calidad del calostro, el metabolismo, el desarrollo y la inmunidad tanto de madres como de cabritos. Si bien es cierto que el incremento del contenido de almidón en la dieta no solo implica modificaciones metabólicas, sino también hormonales (aumento de la insulina en sangre; Haisan et al., 2021), el perfil hormonal de cabras y cabritos no se pudo evaluar en el presente trabajo de investigación debido a limitaciones de tiempo. Asimismo, algunos autores demostraron que la suplementación con almidón puede modificar la proporción de algunos componentes bioactivos en el calostro bovino (oligosacáridos; Hare et al., 2023) los cuales tampoco pudieron ser evaluados.

Los Capítulos 5 y 6 engloban el primer ensayo en el que se emplean los lipopolisacáridos bacterianos como herramienta para favorecer la calostrogénesis. No obstante, el objetivo principal de este experimento fue el de determinar el impacto del LPS sobre la composición del calostro y no sobre la permeabilidad de la barrera sangre-leche (BMB). Aunque los resultados obtenidos puedan ser explicados por una permeabilidad aumentada y/o prolongada de la BMB, para poder afirmar dicha hipótesis hubiese sido necesario, por un lado, obtener una muestra antes del tratamiento para poder establecer un verdadero punto de referencia y, por otro, evaluar otros marcadores de permeabilidad tales como la concentración de lactato deshidrogenasa y albúmina sérica en el calostro y la lactosa en sangre (Wall et al., 2015). Algunos marcadores de inflamación aguda tales como la haptoglobina, el amiloide A sérico, la actividad del sistema de complemento o la población celular en sangre y calostro también podrían haber ayudado a determinar

la severidad de la respuesta inmune local y sistémica. A pesar ser una estrategia novedosa y útil para la mejora de un calostro de poca calidad, la aplicación intramamaria de LPS en el momento del parto también presenta ciertas limitaciones de aplicabilidad en la práctica ganadera. Esta estrategia requiere de una administración completamente estéril inmediatamente después del parto, un retraso en el ordeño y un mayor manejo de los animales. Asimismo, el ensayo experimental fue planteado con el objetivo de estudiar la transferencia de inmunidad y metabolismo en los cabritos neonatos quedando sin evaluar los posibles efectos de una absorción intestinal y respuesta inmune frente a las endotoxinas vehiculizadas en el calostro sobre la salud de éstos.

El Capítulo 7 aporta información relevante en la mejora del bienestar de los animales de producción, una preocupación creciente en la sociedad actual. La codificación y cuantificación de la expresión facial ante estímulos dolorosos supone un avance en el ámbito ganadero y científico dado que permite establecer unos nuevos criterios de bienestar para mejorar la práctica ética en la producción y la investigación. Si bien es cierto, la escala Grimace en cabritos debe seguir evaluándose puesto que el presente estudio no tuvo en cuenta posibles interacciones con factores como la morfología del rostro, el efecto del tiempo o el origen del dolor, ni su posible asociación con el comportamiento del animal.

STRENGTHS AND LIMITATIONS

Chapter 3 highlights the knowledge gaps regarding the physiology and modulation of colostrum production in dairy goats, describing the complex physiological mechanisms involved in this process and demonstrating the impact of certain nutritional strategies, induced immune responses, and the dry-off management on colostrum production. However, the lack of literature on dairy goats still poses a major limitation.

Chapter 4 constitutes the first study evaluating the effect of increased dietary starch during the last month of gestation on colostrum quality, metabolism, development, and immunity of both dams and goat kids. Although an increase in dietary starch triggers both metabolic and hormonal responses (i.e., increased insulin; Haisan et al., 2021), systemic hormones in dams and goat kids, as well as their concentrations on colostrum, could not be evaluated due to time constraints. Additionally, some authors have shown that starch supplementation can modify the concentration of certain bioactive components in bovine colostrum (i.e., oligosaccharides; Hare et al., 2023), which could not be evaluated either in the present study.

Chapters 5 and 6 present the first trial utilizing lipopolysaccharides (LPS) as a tool to enhance colostrum quality. However, the main objective of this experiment was to determine the impact of LPS on colostrum composition and not on the permeability of the blood-milk barrier (BMB). Although the results obtained can be explained by an increased BMB permeability, it would have been necessary to obtain a sample before the LPS treatment to establish a reference value as well as to evaluate other permeability markers such as lactate dehydrogenase and serum albumin concentration in colostrum and lactose in blood (Wall et al., 2015) to confirm this hypothesis. Some acute inflammation markers such as haptoglobin, serum amyloid A, complement system activity, or white cell counts in blood and colostrum could have also helped to determine the severity of the local and systemic immune response. Despite being a novel and useful strategy for improving low-quality colostrum, the intramammary administration of LPS at parturition also entails certain limitations in a practical setting. This strategy requires a sterile administration right after birth, a delay in milking, and greater animal handling. Furthermore, the study was originally planned to address transfer of passive immunity

and metabolism in newborn kids, leaving aside the possible effects of an intestinal absorption and the local and systemic immune response to the LPS present in colostrum.

Chapter 7 constitutes a valuable contribution due to the growing concern for animal welfare in livestock animals. Coding and quantification of facial expression in response to noxious stimuli represents a step forward in both scientific research and animal husbandry. This approach enables the development of novel welfare standards, fostering more ethical practices in livestock management and experimental studies. However, further assessment of the Grimace scale in goats is necessary since the present study did not address potential confounding variables such as facial morphology, type and time exposed to painful stimuli, and its possible association with other welfare indicators.

Perspectivas futuras de la investigación

Future research directions

PERSPECTIVAS FUTURAS DE LA INVESTIGACIÓN

Dadas las limitaciones anteriormente descritas y las posibilidades para dar continuidad a la presente investigación, los futuros estudios podrían integrar otras metodologías de suplementación nutricional (tiempo y nivel de suplementación), uso de fuentes nutricionales alternativas (subproductos locales como los derivados de la producción de cerveza, vino y otras bebidas destiladas) y la combinación de estas con otros nutrientes (proteínas y grasa) durante el período de síntesis de calostro. En cuanto a la administración intramamaria de LPS, podría ser de gran utilidad evaluar los efectos de este tratamiento días antes del parto, ya que de este modo las endotoxinas actuarían durante la calostrogénesis y no al final de ésta. Asimismo, supondría un gran avance evaluar la combinación de ambas estrategias de manera simultánea, adoptando un enfoque multidisciplinar, combinando la biología molecular, la inmunología, la genética, y otras técnicas ómicas como la proteómica o la metabolómica para caracterizar los mecanismos moleculares que regulan la calostrogénesis y el papel de las biomoléculas presentes en el calostro caprino. De igual forma, será esencial para el futuro de la producción animal avanzar en el estudio del bienestar animal, el cual garantizará no solo mejores rendimientos productivos sino también la implementación de prácticas éticas indispensables en la investigación y en el entorno ganadero. La futura investigación podría evaluar la expresión del dolor en cabritos sanos tras una exposición oral al LPS, como estrategia para determinar el impacto de las enfermedades infecciosas en el bienestar animal y desarrollar métodos prácticos para su detección precoz.

FUTURE RESEARCH DIRECTIONS

Given the limitations previously described and the wide possibilities to continue the different lines of research proposed in this PhD thesis, future studies should address other nutritional supplementation methodologies (i.e., timing and level of supplementation), the use of alternative nutritional sources (i.e., local by-products such as those derived from beer, wine, and other distilled beverage production), and their combination with other nutrients (i.e., proteins and fat) during colostrogenesis. Regarding the intramammary administration of LPS, future research should evaluate the effects of this treatment days before parturition, as well as the combination of both strategies simultaneously, adopting a multidisciplinary approach combining molecular biology, immunology, genetics, and other omic techniques such as proteomics or metabolomics. Similarly, it will be essential for the future of animal husbandry to prioritize the study of animal welfare, which will guarantee not only a better performance but also the implementation of ethical practices in farms and research contexts. Future research could address health and pain expression resulting from oral LPS exposure in healthy goat kids, to determine the impact of infectious diseases on animal welfare and develop practical methods for its early detection.

Conclusiones

Conclusions

CONCLUSIONES

1. La calostrogénesis es un proceso fisiológico complejo controlado por mecanismos hormonales y modulado por distintas prácticas de manejo, estrategias nutricionales, y la propia respuesta inmune de la glándula mamaria. La combinación e implementación de estas estrategias durante el período seco podría resultar en una mejora de la calidad del calostro.

2. El incremento del contenido de almidón en la dieta durante el último mes de gestación aumenta la concentración de IgG sin modificar la producción, composición química, recuento de células somáticas (SCC) y grados Brix en el calostro. Asimismo, promueve una movilización grasa más lenta, reduciendo la severidad del balance energético negativo durante el período preparto. Todo ello sin afectar la transferencia de inmunidad pasiva, el crecimiento y el estado metabólico de los cabritos.

3. La administración intramamaria de lipopolisacáridos en cabras lecheras en el momento del parto aumenta la concentración de inmunoglobulinas (IgG e IgM) y del SCC en el calostro, sin afectar al estado inmune y metabólico de estas.

4. La administración intramamaria de LPS en cabras lecheras en el momento del parto no mejora la transferencia de inmunidad pasiva ni el estado metabólico de los cabritos durante el primer mes de vida.

5. La escala Grimace es una técnica no invasiva válida para evaluar el dolor a través de la expresión facial en cabritos lactantes.

CONCLUSIONS

1. Colostrogenesis is a complex physiological process controlled by hormonal mechanisms and modulated by various management practices, nutritional strategies, and the immune response of the mammary gland. The combination of these strategies during the dry period could result in better colostrum quality.

2. Feeding a high-starch diet during the last month of gestation increases the concentration of IgG without modifying the yield, chemical composition, somatic cell count (SCC) and Brix degrees in colostrum. It also promotes slower fat mobilization, reducing the severity of the negative energy balance during the prepartum period, without affecting the transfer of passive immunity, performance and metabolic status of goat kids.

3. Intramammary administration of lipopolysaccharides in dairy goats at parturition increases the concentration of immunoglobulins (IgG and IgM) and SCC in colostrum, without affecting the immune and metabolic status of the dam.

4. Intramammary administration of LPS in dairy goats at parturition does not improve the transfer of passive immunity or the metabolic status of goat kids during the first month of life.

5. The Grimace scale is a valid non-invasive technique for assessing pain through facial expressions in pre-weaned goat kids.

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