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Administración de oxitocina y vía del parto:

Asociación con el cese de la lactancia materna

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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A mis padres

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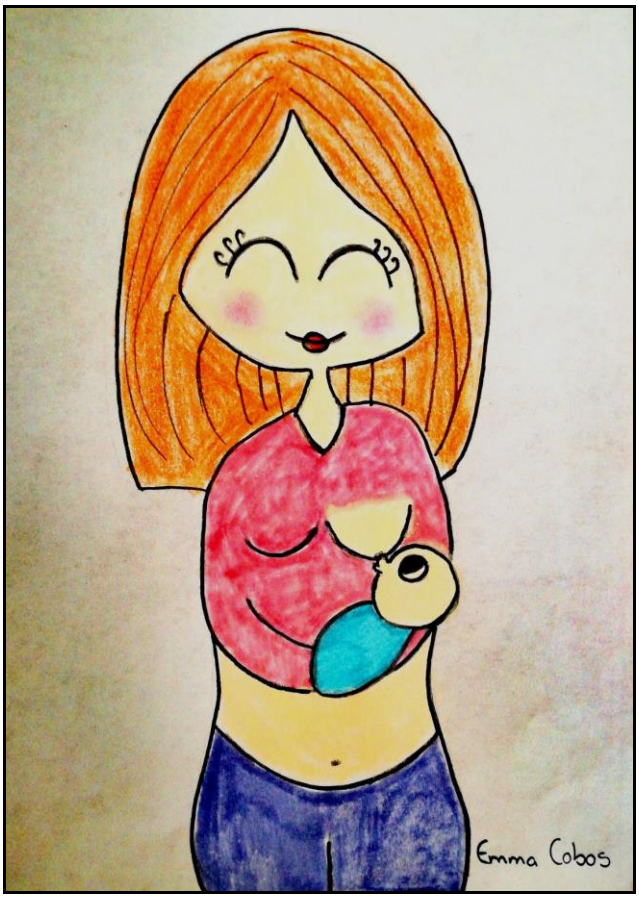


"La observación indica cómo está el paciente; la reflexión indica qué hay que hacer; la destreza práctica indica cómo hay que hacerlo. La formación y la experiencia son necesarias para saber cómo observar y qué observar; cómo pensar y qué pensar."

Florence Nightingale, 1882

RESUMEN

La administración de oxitocina sintética durante el parto y la vía del parto pueden asociarse con el cese de la lactancia materna.

Objetivos: estudiar si la administración de oxitocina sintética intraparto se asocia con el cese de la lactancia materna exclusiva a los 3 y 6 meses de vida. Los objetivos secundarios son investigar si la vía del parto y los factores del parto y sociodemográficos se asocian con el cese de la lactancia materna exclusiva en los periodos estudiados.

Metodología: estudio de cohortes prospectivo (n=529) realizado en un hospital terciario. Se incluyeron gestaciones únicas a término. Se establecieron 4 grupos según la vía del parto (vaginal o cesárea) y la administración de oxitocina intraparto. Se hizo seguimiento para evaluar el mantenimiento de lactancia materna exclusiva a los 3 y 6 meses.

Resultados: durante el seguimiento, la proporción de lactancia materna exclusiva disminuyó en todos los grupos. Tras realizar un análisis ajustado por variables de confusión, se observó que el grupo de cesáreas sin oxitocina (cesáreas programadas) tenía mayor riesgo de cese de la lactancia materna exclusiva a los 3 y 6 meses (odds ratio [intervalo de confianza 95%], 2.51 [1.53-4.12]). No se observó asociación entre la dosis de oxitocina administrada en el parto y el puerperio y el cese de la lactancia materna exclusiva.

Conclusiones: la administración de oxitocina durante el parto no se asocia con el cese de la lactancia materna exclusiva a los 3 y 6 meses de vida. El parto mediante cesárea programada (sin oxitocina) se asocia con el cese de la lactancia materna exclusiva en los periodos estudiados. La ausencia de estudios universitarios, el uso de chupete y la no asistencia a grupo de apoyo a la lactancia materna se asocian con el cese de la lactancia

materna exclusiva a los 3 meses. La primiparidad, el uso de chupete y la incorporación laboral se asocian con el cese de la lactancia materna exclusiva a los 6 meses de vida.

Palabras clave: lactancia materna exclusiva, oxitocina, vía del parto.

SUMMARY

The administration of synthetic oxytocin during labor and the mode of delivery can be associated with cessation of breastfeeding.

Objectives: to study whether the intrapartum administration of synthetic oxytocin is associated with cessation of exclusive breastfeeding at 3 and 6 months of life. The secondary objectives are to investigate whether the mode of delivery and the labor and sociodemographic factors are associated with cessation of exclusive breastfeeding in the periods studied.

Methods: prospective cohort study (n = 529) conducted in a tertiary hospital. Only full-term singleton pregnancies were included. Four groups were established based on the mode of delivery (vaginal or cesarean) and the intrapartum administration of oxytocin. Follow-up was performed to evaluate the consolidation of exclusive breastfeeding at 3 and 6 months.

Results: during follow-up, the proportion of exclusive breastfeeding decreased in all groups. After adjusting for confounding variables, the group with cesarean delivery without oxytocin (planned cesarean delivery) had the highest risk of cessation of exclusive breastfeeding at 3 and 6 months (odds ratio [95% confidence interval], 2.51 [1.53-4.12]). No association was found between the oxytocin dose administered during labor and the puerperium and the cessation of exclusive breastfeeding.

Conclusions: oxytocin administration during labor is not associated with cessation of exclusive breastfeeding at 3 and 6 months of life. Planned cesarean delivery without

oxytocin is associated with the cessation of exclusive breastfeeding in the periods studied. No college degree, pacifier use and the not attending breastfeeding support groups are associated with the cessation of exclusive breastfeeding at 3 months. Primiparity, pacifier use and re-integration into the workplace are associated with the cessation of exclusive breastfeeding at 6 months of life.

Keywords: exclusive breastfeeding, oxytocin, mode of delivery.

INTRODUCCIÓN

Lactancia materna

Importancia y beneficios de la lactancia materna

La lactancia materna exclusiva (LME) durante los primeros 6 meses de vida aporta muchos beneficios tanto al niño como a la madre[1].

En el niño, la lactancia materna (LM) se asocia con una reducción de la incidencia de otitis, gastroenteritis, infecciones respiratorias, dermatitis, asma, obesidad, diabetes, leucemia, enterocolitis y síndrome de muerte súbita. En la madre, además de beneficios afectivos, psicológicos y de vínculo, la LM se asocia con una disminución del riesgo de padecer diabetes, cáncer de mama y cáncer de ovario[2].

A nivel social, la alimentación con leche materna supone un ahorro en la compra de fórmulas infantiles así como una reducción del número de consultas y hospitalizaciones debidas a procesos infecciosos agudos durante la lactancia. Además, su uso es seguro porque no está sujeto a contaminación ni a errores en su preparación[3].

La leche materna también es una fuente importante de energía y nutrientes para los niños de 6 a 23 meses. Puede aportar más de la mitad de las necesidades energéticas del niño entre los 6 y los 12 meses, y un tercio entre los 12 y los 24 meses[1].

La Organización Mundial de la Salud (OMS) recomienda la LME durante los primeros 6 meses, la introducción de alimentos seguros y apropiados para la edad a partir de entonces, y el mantenimiento de la LM hasta los 2 años o más[4].

Fisiología de la lactancia materna

El funcionamiento de la mama, a diferencia de otros órganos, no depende solo de las estructuras anatómicas u hormonales de la madre, sino que requiere el vaciado activo por parte del lactante.

La lactogénesis es el proceso que origina la secreción de leche y se desarrolla en varias fases:

- Lactogénesis I. A partir del 5º mes de embarazo, la mama fabrica pequeñas cantidades de leche y las células mamarias producen lactosa y α-lactoalbúmina que se detectan en sangre y orina.
- Lactogénesis II. Tras el parto, se produce un descenso brusco de la progesterona, y por tanto, se suprime su acción inhibidora sobre la prolactina. Entonces se produce un aumento masivo de la síntesis de leche. Aunque la prolactina es la hormona promotora de la lactancia, existen hormonas coadyuvantes necesarias para que se establezca la secreción: oxitocina, hormonas tiroideas, hormona de crecimiento, insulina y corticoides (Figura 1).

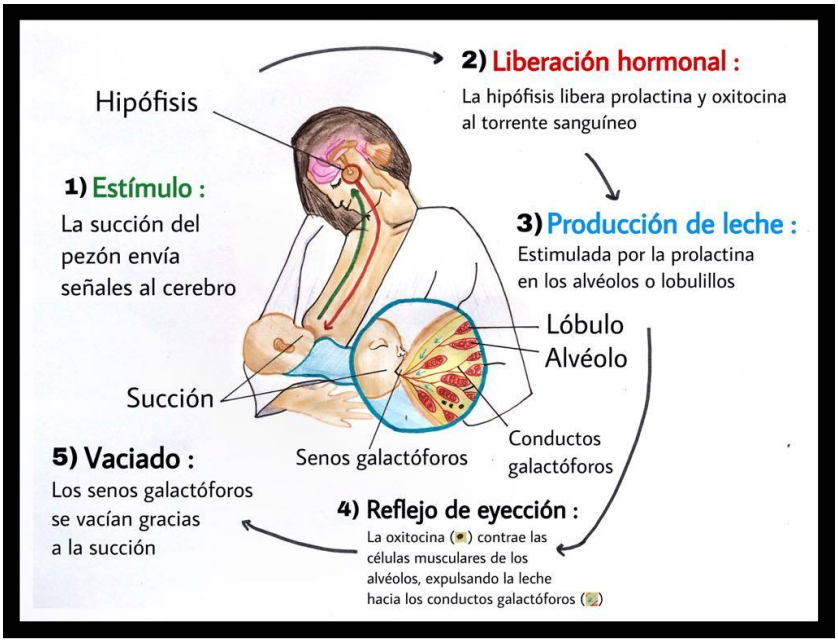


Figura 1. Fisiología de la LM

La hormona oxitocina se libera en respuesta al estímulo del pezón (succión). Dicho estímulo alcanza por diferentes vías los núcleos supraóptico y paraventricular del hipotálamo, donde se produce esta hormona, que es almacenada y liberada por la

neurohipófisis. La oxitocina llega a la mama por vía sanguínea y estimula los receptores específicos de las células mioepiteliales, cuya contracción provoca la salida de leche del alveolo, facilitando su desplazamiento por los conductos hacia el pezón.

Los receptores oxitócicos de las fibras mioepiteliales de mama, útero y vagina aumentan en número durante el tercer trimestre del embarazo y tras el parto. Ésto favorece la sensibilidad a la oxitocina segregada durante la lactancia. El estrés, la ansiedad, el dolor y otros estímulos físicos desagradables pueden bloquear el reflejo de eyección (reflejo neuro-hormonal).

La galactopoyesis es el proceso de mantenimiento de la LM una vez iniciada y establecida. La succión y vaciado frecuentes de la mama son absolutamente necesarios para asegurar una adecuada producción de leche. Por lo tanto, el funcionamiento correcto de la mama depende tanto del sistema hormonal como del vaciado de la mama[5].

Inicio de la lactancia materna. Contacto precoz madre-recién nacido

Durante las dos primeras horas después del nacimiento, el recién nacido está en alerta tranquila; es el llamado periodo sensitivo, provocado por la descarga de noradrenalina que tiene lugar durante el parto.

Por ello, nada más nacer se recomienda colocar al recién nacido en contacto piel con piel con la madre dados los múltiples efectos beneficiosos para ambos:

- Facilita reconocer el olor materno, establecer el vínculo, la lactancia y la adaptación a la vida extrauterina.
- Se recuperan más rápido del estrés, normalizan antes su glucemia, el equilibrio ácido-base y la temperatura.
- Pone en marcha los reflejos de búsqueda y succión, aumentando la frecuencia de tomas con éxito.

- Para la madre facilita la disminución del tamaño uterino por secreción de oxitocina y evita experiencias emocionales negativas[2].

Si nada más nacer se deja al recién nacido en decúbito prono en contacto piel con piel, poco a poco va reptando hacia los pechos de su madre mediante movimientos de flexión y extensión de las extremidades inferiores, toca el pezón, pone en marcha los reflejos de búsqueda, se dirige hacia la areola, que reconoce por su olor y la succiona correctamente. A partir de entonces, es más probable que haga el resto de tomas con un agarre adecuado[5].

Parto

Definición

Se denomina parto al proceso fisiológico que pone fin al embarazo haciendo que el feto y sus anejos abandonen el útero y salgan al exterior.

Factores del parto

En el parto intervienen tres fuerzas o factores:

- Motor del parto. Está constituido por las contracciones uterinas reforzadas en cierto momento por la presión de la prensa abdominal.
- Objeto del parto. El feto y los anejos fetales que han de ser llevados al exterior.
- Canal del parto. El camino que el feto debe recorrer desde el interior del útero hasta su salida de la madre.

Causas del parto

El parto es el resultado de la expresión de un conjunto de sucesos interrelacionados; cada uno de ellos afecta al otro, pero ninguno por sí mismo puede ser considerado absolutamente esencial:

- Al final del embarazo se produce la maduración definitiva del feto, lo que le pone en condiciones de vivir autónomamente en el exterior del claustro materno.

Se estimula la activación del eje hipófiso-suprarrenal fetal, con intervención de la hormona liberadora de corticotropina (CRH) placentaria y producción de cortisol adrenal fetal.

- La CRH placentaria, el sulfato de dehidroepiandrosterona (DHEA-S) fetal y otras sustancias de los tejidos placentarios y de las membranas ovulares llevan a un desequilibrio entre estrógenos y progesterona con predominio de los primeros y supresión del bloqueo progesterónico del útero.
- El nuevo ambiente hormonal permite la síntesis de prostaglandinas, que determinan el inicio de las contracciones.
- El aumento registrado en los receptores miometriales de oxitocina condiciona la sensibilización del mismo a esta hormona, que es decisiva en el mantenimiento de las contracciones del parto.

Periodos del parto

En todo parto que evolucione por vía vaginal se suceden tres periodos:

- Periodo de dilatación. Transcurre desde su comienzo hasta que se produce la dilatación completa del cuello.
- Periodo expulsivo. Transcurre entre el final de la dilatación del cuello uterino y la salida total del feto al exterior.
- Periodo de alumbramiento. Una vez terminada la expulsión fetal, se produce la separación o desprendimiento de los anejos fetales del útero y su expulsión al exterior.

Inducción del parto

Se entiende por inducción del parto la instauración artificial de contracciones uterinas con el fin de terminar la gestación cuando el feto es viable. La inducción se logra más fácilmente cuanto más avanzado esté el embarazo.

Se puede distinguir entre:

- Inducción médica, motivada o indicada por razones maternas, obstétricas o fetales. La gestación cronológicamente prolongada (GCP) y la rotura prematura de membranas (RPM) son las situaciones clínicas que más frecuentemente justifican la inducción del parto.
- Inducción electiva, justificada por razones de tipo menor, como por ejemplo, partos anteriores muy rápidos que hagan temer dificultades para llegar al hospital, o por razones de índole estrictamente social o de conveniencia.

La inducción del parto no es procedimiento exento de riesgos. Por lo tanto, su realización estará justificada siempre y cuando el feto o la madre se beneficien con la terminación del embarazo.

Los principales métodos de inducción son:

- Despegamiento de las membranas fetales o maniobra de Hamilton.
- Medios mecánicos como la colocación de una sonda/ balón a nivel del cuello uterino.
- Amniotomía o rotura artificial de las membranas a nivel del polo inferior con ayuda de una lanceta.
- Administración de oxitocina por vía intravenosa. Es el método más empleado para inducir el parto.
- Empleo de prostaglandinas a través de la vagina para provocar la maduración del cuello uterino.

Cesárea

La operación cesárea es la intervención obstétrica mediante la cual se extrae el feto, la placenta y las membranas a través de una laparotomía seguida de histerotomía.

En la actualidad, es la intervención obstétrica más frecuente, por considerarse que es la forma más segura de resolver la mayoría de las distocias y de preservar la integridad fetal, no solo durante el parto, sino en muy diferentes circunstancias del embarazo[6].

La cesárea programada o electiva es la que se realiza antes del inicio de parto, por razones maternas, fetales o ambas; las condiciones obstétricas no aconsejan esperar hasta el inicio del parto.

Los neonatos nacidos mediante cesárea tienen una mayor incidencia de morbilidad respiratoria que los nacidos mediante parto vaginal. Además, la morbilidad neonatal es mayor en las cesáreas programadas que en las cesáreas urgentes realizadas cuando se ha iniciado el trabajo de parto. En comparación con los recién nacidos mediante cesárea urgente, los neonatos nacidos mediante cesárea programada tienen un aumento significativo del riesgo de morbilidad respiratoria a cualquier edad gestacional antes de la semana 40. El riesgo de iatrogenia neonatal en las cesáreas electivas en la semana 37-38 (recién nacido a término temprano) debe de ser cuidadosamente sopesado a la hora de programar la cesárea. Por ello, la Sociedad Española de Ginecología y Obstetricia (SEGO) considera que las cesáreas electivas se deben programar a partir de la semana 39 de gestación para evitar la morbilidad neonatal, fundamentalmente respiratoria[7].

Las indicaciones de la cesárea han variado a lo largo de la historia, pasando de ser una intervención que se realizaba únicamente en situaciones extremas con la finalidad de salvar la vida de la madre, a ser objeto de debate su realización por deseo materno sin que exista indicación médica.

La incidencia de cesáreas experimentó un incremento espectacular en las últimas décadas del siglo XX. Así, en el Hospital Universitario La Paz de Madrid, se pasó del 3.88% en 1970 al 15.54% en 1994 y al 26.61% en 2016. En el Hospital Universitario 12

de Octubre de Madrid, la incidencia del 8.8% de 1981 se elevó al 18% en 1994 y al 21.69% en 2016[6,8].

En primer lugar, el aumento de las cesáreas se debe a la disminución de los riesgos inherentes a su práctica por los avances registrados en anestesia y técnica quirúrgica. Después, a la creencia generalizada de que la cesárea ofrece mayor seguridad para el feto y evita la mayoría de los problemas que se presentan durante el parto.

El control del parto mediante cardiotocografía conlleva una serie de resultados falsos positivos que hay que saber interpretar y favorece de forma injustificada el incremento de cesáreas. Además, la práctica obstétrica se ha hecho muy activa, indicándose cada vez con más frecuencia la interrupción del embarazo en casos de preeclampsia, crecimiento intrauterino retardado (CIR) o gestación prolongada, e incluso en muchos casos de parto pretérmino, con el consiguiente aumento de cesáreas.

Asimismo, la mayor incidencia de partos múltiples debida a la generalización de las técnicas de reproducción asistida, aumenta la proporción de cesáreas ante el temor de complicaciones en mujeres que quizá consiguieron su embarazo con técnicas complejas y después de años de espera.

La cesárea puede evitar muchas reclamaciones y complicaciones legales. Las demandas judiciales ante resultados no deseados favorecen la práctica de una medicina defensiva, y una faceta de ésta puede ser la realización de una cesárea[6].

Por último, es difícil establecer la incidencia real de la cesárea por deseo materno debido a que la evidencia de estudios prospectivos y retrospectivos es limitada, utilizando diferentes definiciones y publicando incidencias dispares que van del 1% al 48% para hospitales del sector público y del 60% en hospitales del sector privado.

En nuestro entorno, el 70% de las cesáreas son primeras cesáreas; sus indicaciones más frecuentes son:

- Distocia (65%)
- Presentación anómala (15%)
- Riesgo de pérdida del bienestar fetal (RPBF) (10%)

Estas tres indicaciones engloban el 90% de las cesáreas primarias[7].

Una cesárea realizada en el primer parto predispone a repetirla en los siguientes, con lo que se crea una espiral de aumento de cesáreas. En este sentido, la SEGO considera que se debe ofrecer un intento de parto por vía vaginal a todas las mujeres con cesárea previa, una vez que se descarten las contraindicaciones y se informe a la gestante de los riesgos y beneficios del parto vaginal[9].

Las posibles consecuencias tardías que la cesárea programada puede tener sobre el cerebro de la madre y el recién nacido no han sido estudiadas en profundidad. Cuando se realiza una cesárea programada, la transición neurohormonal es bastante aguda y difiere mucho de la cascada neuroendocrina que tiene lugar durante el parto vaginal. Así, los recién nacidos mediante cesárea programada tienen menores niveles de vasopresina, catecolaminas y cortisol, hormonas relacionadas con el control térmico y glucémico tras el nacimiento, o el reconocimiento olfatorio entre otros[10].

Experimentos en ratones sugieren que la omisión del trabajo de parto puede afectar el desarrollo cerebral de la descendencia. Simón-Areces et al[11] compararon ratones nacidos por parto vaginal con ratones nacidos por cesárea electiva. Analizaron el tamaño y la función de su hipocampo, especialmente midiendo la producción de la proteína de desacoplamiento mitocondrial 2 (UCP2), que es fundamental para la utilización de ácidos grasos por parte de las neuronas adultas. Posteriormente observaron cómo se comportaban los ratones en la edad adulta a través de experimentos que medían su memoria espacial y su conducta ante una situación estresante. Los nacidos por cesárea programada mostraban déficits significativos en ambas situaciones,

así como menos proteína UCP2 en el hipocampo, menos neuronas, más pequeñas y con menos conexiones.

Oxitocina

La oxitocina es un polipéptido, cuya estructura consiste en una secuencia de nueve aminoácidos. Es producida principalmente por el núcleo paraventricular del hipotálamo y secretada por el lóbulo posterior de la hipófisis o neurohipófisis de forma pulsátil.

La oxitocina es una hormona importante en la fisiología femenina. Se libera durante el coito provocando contracciones uterinas en el orgasmo, interviene en la ovulación y, sobre todo, desempeña un papel fundamental en el parto y durante la lactancia[6].

Sus receptores específicos se encuentran en el miometrio y las glándulas mamarias, y aparecen durante el embarazo. También existen receptores en diversas áreas del sistema nervioso central tales como el área preóptica del hipotálamo, la amígdala y la ínsula[12].

La hormona oxitocina favorece y controla la contracción uterina. Es liberada en pequeñas cantidades y en flujo discontinuo a lo largo del parto. Como su vida media es breve y su liberación es escasa, las cantidades circulantes en sangre son pequeñas. Por ello, es fundamental que la sensibilidad miometrial sea óptima, y ésta se consigue cuando el número de receptores de oxitocina del miometrio alcanza un punto crítico.

En la liberación de oxitocina desde la hipófisis posterior se establece un reflejo nervioso a partir del propio útero. La presión de la cabeza fetal sobre el cuello uterino desencadena un arco reflejo que, a través de la médula, llega al hipotálamo y la hipófisis posterior (reflejo de Ferguson). De esta manera, se asegura la continuidad y el refuerzo de las contracciones una vez iniciado el parto.

La oxitocina de origen fetal también tiene un papel importante en el inicio y el mantenimiento del parto. En la sangre de la arteria umbilical hay mayor concentración de oxitocina que en la sangre de la vena umbilical, lo que confirma su procedencia fetal.

Por lo tanto, la liberación pulsátil de oxitocina por la hipófisis posterior fetal es una demostración de la participación del feto en el proceso de su parto[6] (Figura 2).

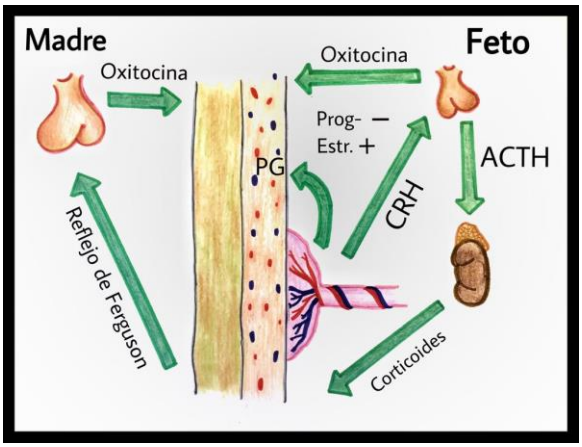


Figura 2. Fisiología de la oxitocina en el parto

El inicio de la lactancia, la eyección de leche y el inicio del vínculo también dependen entre otras cosas de la secreción pulsátil de oxitocina desde la hipófisis posterior[13,14], junto con la síntesis de oxitocina por parte las células mioepiteliales mediante un mecanismo local de feedback positivo[15]. En situaciones de estrés como la pérdida de sangre abundante, el parto prolongado o la cesárea, la secreción pulsátil de oxitocina se sustituye por una secreción continua que reduce la estimulación de las células mioepiteliales[16,17].

La oxitocina parece ser la hormona mediadora de la conducta maternal en los mamíferos. El aumento fisiológico de oxitocina en el cerebro materno tras el parto produce en la madre una sensación de euforia, sueño más ligero y aumento del umbral del dolor, así como un incremento de la sensación de cariño hacia su hijo y disminución de la sensación de estrés mediante la reducción, entre otros, de los niveles de cortisol. Los niveles de oxitocina se encuentran más aumentados en aquellas mujeres que mantienen a sus hijos en contacto piel con piel y asimismo, presentan nuevas elevaciones de esta hormona en relación con los periodos de amamantamiento[18]. Ambos

procesos (contacto piel con piel y succión) pueden por tanto favorecer el apego de las madres por sus hijos por elevación de la oxitocina, además de mejorar el tono uterino tras el parto y disminuir la posibilidad de sangrado puerperal.

La oxitocina endógena se libera de forma pulsátil y creciente a lo largo del parto fisiológico, alcanzándose los niveles máximos en cerebro materno en la hora que sigue al parto[16]. Este fenómeno se ha asociado con la existencia de un período sensitivo temprano durante el cual se produce un escenario neurohormonal específico tanto en el cerebro materno como en el del recién nacido destinado a facilitar el inicio del vínculo materno filial, con algunas características similares a la impronta observada en otras especies[19,20].

En los nacimientos mediante cesárea programada, sin trabajo de parto previo, no se produce el pico de oxitocina endógena. En trabajos experimentales con mamíferos se ha observado que las hembras que dan a luz por cesárea programada pueden mostrarse indiferentes hacia la cría recién nacida, hecho que se ha relacionado con la ausencia de oxitocina endógena. Se ha especulado que las mujeres que no presentan este aumento de oxitocina endógena podrían igualmente mostrarse indiferentes hacia el cuidado de los hijos o tener más dificultades en la interacción temprana con el lactante[21].

Oxitocina sintética, vía del parto y LM: antecedentes y estado actual del tema

En España, no existe un sistema oficial de monitorización de la LM. Sin embargo, diversos trabajos publicados en la última década indican que la frecuencia y duración de la LM no alcanza el patrón óptimo recomendado por la OMS[22,23].

Según la última Encuesta Nacional de Salud elaborada por el Instituto Nacional de Estadística entre los años 2011 y 2012, el porcentaje de lactancia natural es del 53% a los 3 meses de vida y del 28% a los 6 meses de vida[24]. Entre los resultados del estudio prospectivo con 452 diadas madre-hijo realizado por Rius et al en una región del este de

España en 2005, se recoge que el mantenimiento de la LM a los 3 y 6 meses es del 39 y 21% respectivamente[23]. En otros países de la Unión Europea, las tasas de LME a los 6 meses son del 34% (Portugal), 17.2% (Dinamarca), 14% (Suecia) y 5% (Italia)[25].

Dados los probados beneficios de la LM, es importante identificar aquellos factores que pueden conducir a su abandono y a la introducción de suplementos. Estudios previos muestran que algunos factores del parto, tales como la vía del parto y la administración de oxitocina, pueden afectar el curso de la LM[26,27].

Diversas manipulaciones en el período perinatal pueden alterar el escenario neurohormonal fisiológico tanto de la madre como del bebé. Factores como la cesárea programada, la inducción del parto con oxitocina sintética o el parto detenido por antagonistas oxitocinérgicos como el atosibán alteran el equilibrio de oxitocina y vasopresina en el recién nacido. En el mismo sentido, tanto la ausencia de contacto precoz piel con piel o la separación madre-recién nacido como la lactancia artificial (LA) conllevan una disrupción de la liberación de oxitocina endógena materna sin que se conozcan en profundidad los efectos a medio y largo plazo de estas manipulaciones en humanos[28]. En otros mamíferos, los efectos de la manipulación peptídica perinatal en las crías han sido estudiados e incluyen cambios a largo plazo en la conducta social y sexual[29]. Además se ha comprobado que los efectos son diferentes en función del sexo de la cría[28].

Durante el trabajo de parto, es frecuente recurrir a la administración de oxitocina sintética con el fin de mantener una dinámica uterina eficaz[30]. Asimismo, la oxitocina sintética es el fármaco de elección para la inducción del parto, cuyo objetivo es intentar que éste tenga lugar por vía vaginal cuando hay indicación médica de finalizar la gestación y el parto no se ha desencadenado de forma espontánea.

También es cierto que la maduración cervical con prostaglandinas en el caso de cérvix desfavorable y las medidas mecánicas encaminadas a reforzar la acción de la oxitocina sintética durante la inducción de parto (maniobra de Hamilton y amniorrexis artificial) pueden contribuir a disminuir las dosis de oxitocina administrada.

Hay una tendencia a asumir que los efectos de la oxitocina exógena son bien conocidos y benignos. Sin embargo, es el fármaco que más frecuentemente se asocia con efectos adversos prevenibles o evitables durante el parto[31].

Cuando la oxitocina se administra a dosis elevadas mediante infusión intravenosa para la inducción del parto, produce una sobreestimulación uterina que puede causar sufrimiento fetal, asfixia y muerte, o puede conducir a hipertonicidad, contracciones tetánicas o rotura del útero. La inyección intravenosa rápida en bolo de oxitocina a dosis que ascienden a varias UI, puede provocar una hipotensión aguda de corta duración acompañada de rubefacción y taquicardia refleja. Estos cambios hemodinámicos repentinos pueden dar lugar a isquemia de miocardio, particularmente en pacientes con enfermedad cardiovascular preexistente. Este modo de administración, también puede dar lugar a la prolongación del intervalo QT.

En raras ocasiones, se ha descrito un aumento del riesgo de coagulación intravascular diseminada (CID) después del parto en pacientes sometidas a inducción farmacológica del parto con agentes uterotónicos. Se ha notificado intoxicación hídrica asociada a hiponatremia materna y neonatal en casos en que se administraron altas dosis de oxitocina junto con grandes cantidades de líquidos sin electrólitos durante un periodo prolongado de tiempo. El efecto antidiurético combinado de la oxitocina con la administración intravenosa de líquidos puede causar sobrecarga de líquidos dando lugar a una forma hemodinámica de edema pulmonar agudo sin hiponatremia[32].

Aunque el impacto de la oxitocina exógena en la conducta y en la LM no ha sido estudiado en profundidad[21], se sabe que puede aumentar o imitar la respuesta de estrés, interrumpir la secreción pulsátil de oxitocina y la actividad subsiguiente de las células mioepiteliales necesaria para el inicio de la LM[16,33], alterar las señales en el receptor de oxitocina de las células mioepiteliales y endoteliales[34], estimular y luego vaciar las neuronas que segregan oxitocina[35,36], y alterar el balance de oxitocina y los cambios en la arquitectura neuronal en el periodo sensitivo del nacimiento, afectando a la adaptación maternal[37,38].

En síntesis, la oxitocina exógena puede alterar el inicio de la LM mediante: alteración de la secreción pulsátil de oxitocina y de las oscilaciones de la concentración, desensibilizacion de los receptores, y de manera más especulativa, alterando la conducta infantil o maternal. Asimismo, la administración de oxitocina intraparto produce una disminución de los niveles de oxitocina en el segundo día del puerperio y un aumento de la prolactina[27].

A nivel de la conducta del lactante, asumir que la manipulación perinatal con oxitocina no tiene efectos es algo por demostrar y los pocos estudios en animales señalan que esta afirmación probablemente sea inválida[21]. Los experimentos con perritos de las praderas han mostrado como la manipulación del sistema oxitocinérgico en el período perinatal puede producir cambios de por vida en las conductas de apego y en las conductas sociales, incluyendo el emparejamiento de los adultos y las conductas parentales así como la reactividad del eje HPA, hallazgos que se han repetido en otros mamíferos[29].

Se considera que existen dos barreras que evitan el paso potencial de oxitocina al cerebro del feto:

- La barrera materno-placentaria. La barrera placentaria tiene oxitocinasas que parecen efectivas degradando la oxitocina.

Algunos estudios sobre la difusión materno-fetal y feto-materna de oxitocina han encontrado que el transporte es mayor en dirección madre-feto. Es decir, la oxitocina sintética administrada a la madre puede llegar a la circulación fetal[39].

- La barrera hematoencefálica (BHE) del feto. Durante tiempo se pensó que la oxitocina no podía atravesar la BHE, pero se han encontrado excepciones[40].

  Durante el parto, la situación de estrés experimentada por madre e hijo puede causar un aumento de la liberación de citoquinas (estrés oxidativo), que hace que la BHE sea más permeable de lo habitual. En síntesis, la oxitocina sintética administrada a la madre puede llegar al cerebro del feto[41].

Diversos estudios han demostrado a su vez que el exceso de oxitocina circulante puede desensibilizar los receptores de oxitocina por diversos mecanismos, y por tanto, disminuir los efectos beneficiosos derivados de su actuación.

Del mismo modo, el parto mediante cesárea implica una manipulación habitual de la neurobiología del parto. En las situaciones de cesárea programada, la dinámica uterina ocasionada por la liberación pulsátil de oxitocina que sí tiene lugar en el parto vaginal, no se lleva a cabo. Tampoco tiene lugar el descenso de la cabeza fetal a través del canal del parto, que supone un estímulo importante para la liberación de oxitocina materna (reflejo de Ferguson). Igualmente, al no producirse la compresión de la cabeza fetal por el canal del parto, el recién nacido no libera las sustancias (catecolaminas y cortisol) responsables de modificar el nivel de alerta en las primeras horas de vida.

Son diversos los estudios en los que se observa cómo la respuesta de las madres a las necesidades del recién nacido son distintas en función de la vía del parto. Además, existen diversas investigaciones que aseveran que la cesárea puede suponer una reducción de las tasas de LM, si bien en muchas ocasiones se añade al mecanismo neurohormonal citado, otras situaciones que no siempre son fáciles de controlar en los

estudios de investigación (tales como separación madre-recién nacido o no realización de contacto precoz piel con piel) y que pueden influir en las conclusiones establecidas[10].

Algunos autores han estudiado cómo la inducción del parto puede retrasar el inicio de la LM, si bien no han examinado los efectos que puede tener sobre la duración de la misma[42]. Asimismo, un estudio retrospectivo llevado a cabo en España apunta que la inducción del parto mediante la administración de oxitocina se asocia con una mayor dificultad en el inicio y mantenimiento de la LM[43].

En contraste con estos resultados, un estudio prospectivo multicéntrico realizado en Hong Kong concluye que intervenciones como la inducción del parto, la administración de fármacos opioides, la analgesia epidural o la vía del parto no influyen en la LM, si bien considera que la coincidencia de múltiples intervenciones incrementa el riesgo de abandono de la LM[44].

En relación con esta hipótesis de estudio, el grupo de Neurobiología del Apego del Hospital Universitario Puerta de Hierro de Majadahonda llevó a cabo un primer estudio con el objetivo principal de valorar la repercusión de la administración de oxitocina intraparto sobre las conductas de apego del recién nacido.

Las conclusiones del estudio fueron las siguientes:

- Se observó una relación inversa entre la administración de oxitocina intraparto y el porcentaje de reflejos neonatales primitivos del recién nacido[45] (Apéndice 1).
- La administración de dosis superiores a 2000 mU de oxitocina durante el trabajo de parto podía influir en el tipo de lactancia al mes y los 3 meses de vida[45].
- Se observó una relación inversa entre la administración de oxitocina exógena y el porcentaje de LME al mes y los 3 meses[46] (Apéndice 2).

- Eran necesarios más estudios que investigasen la repercusión de la administración de oxitocina intraparto sobre las conductas de apego del recién nacido.

Para continuar con la línea de investigación iniciada, se desarrolló el proyecto *Efectos de la oxitocina endógena y exógena en las conductas de apego del recién nacido y en la interacción social en el segundo año de vida*, financiado por el Instituto de Salud Carlos III con el número de expediente PI10/00791.

Los objetivos secundarios de dicho proyecto de investigación eran estudiar el efecto de la administración de oxitocina intraparto en el inicio y mantenimiento de la LM y estudiar el efecto de la vía del parto en la LM.

Algunas de las conclusiones fueron:

- La administración de oxitocina intraparto podía inhibir la expresión de reflejos neonatales primitivos asociados con la LM. Dicha correlación no parecía dosis dependiente[47] (Apéndice 3).
- No se observó asociación estadísticamente significativa entre la administración de oxitocina sintética durante el parto y el inicio y mantenimiento de la LM al mes, los 3 meses y los 6 meses[48].
- Dada la falta de conocimiento acerca de la asociación entre la oxitocina sintética y la LM, sería deseable que esta relación fuese investigada en futuros estudios.

A partir de los resultados de este proyecto, el grupo de Neurobiología del apego amplió la investigación con el objetivo de profundizar en el conocimiento de las repercusiones de la administración de oxitocina sintética y la vía del parto en el éxito de la LM.

Dado que el inicio y mantenimiento de la LM también podía verse influido tanto por otros factores del parto como por factores sociodemográficos, en el siguiente proyecto, objeto de la presente tesis doctoral, se incluyó el estudio de los siguientes factores:

- Factores del parto: administración de oxitocina sintética, vía del parto y analgesia epidural[26,27].
- Factores sociodemográficos[49]: edad materna, estudios no universitarios, nuliparidad, edad gestacional, ausencia de educación prenatal, sexo del recién nacido, uso de chupete, no asistencia a grupo de apoyo a la LM e incorporación laboral[50].

HIPÓTESIS

La administración de oxitocina sintética durante el parto y la vía del parto pueden asociarse con el cese de la LM.

OBJETIVOS DE LA INVESTIGACIÓN

Objetivo principal

- Estudiar si la administración de oxitocina sintética intraparto se asocia con el cese de la LME a los 3 y 6 meses de vida.

Objetivos secundarios

- Estudiar si la vía del parto se asocia con el cese de la LME a los 3 y 6 meses de vida.
- Estudiar si factores del parto y sociodemográficos se asocian con el cese de la LME a los 3 y 6 meses de vida.

METODOLOGÍA Y PLAN DE TRABAJO

Diseño: tipo de estudio

Estudio de cohortes prospectivo (n=529) realizado en un hospital terciario con Galardón Iniciativa para la Humanización de la Asistencia al Nacimiento y la Lactancia (IHAN) y más de 3000 partos al año (Hospital Universitario Puerta de Hierro de Majadahonda).

Aprobado por el Comité Ético de Investigación Clínica (CEIC) del centro hospitalario (Anexo 1).

Criterios de inclusión

- Gestaciones únicas a término.
- Test de Apgar a los 5 minutos >7.
- Deseo prenatal de administrar LM.
- Firma del consentimiento informado antes del parto (Anexo 2).

Criterios de exclusión

- Recién nacido pretérmino.
- Cromosomopatías fetales u otras anomalías diagnosticadas intraútero que modifiquen la adaptación al medio extrauterino.
- Ingreso de la madre en Unidad de Cuidados Intensivos.
- Ingreso del recién nacido en la Unidad de Neonatología las primeras 48 horas de vida.
- Deseo expreso de dar lactancia artificial.
- En caso de cesárea, administración de anestesia general a la madre.
- Dificultades en el idioma.

Cálculo del tamaño muestral

Para conseguir una potencia del 80% para detectar diferencias en el contraste de la hipótesis nula H_o:p1=p2 mediante una prueba Chi cuadrado bilateral para dos muestras

independientes, teniendo en cuenta que el nivel de significación es del 5%, y asumiendo, de acuerdo con un estudio previo de nuestro grupo de investigación (PI10/00791), que la proporción de abandonos en la cohorte expuesta (grupos pv+ox y c+ox) es del 46%, en la cohorte no expuesta (grupos pv-ox y c-ox) es del 34%, y que la proporción de pacientes en la expuesta vs la no expuesta respecto el total es del 55% , sería necesario incluir:

- 294 participantes en la cohorte expuesta (grupos pv+ox y c+ox)
- 235 participantes en la cohorte no expuesta (grupos pv-ox y c-ox).

Procedimiento de captación y estudio

El trabajo se desarrolló secuencialmente a lo largo de 22 meses, desde febrero de 2015 hasta diciembre de 2016:

- La captación de pacientes fue llevada a cabo durante los 16 primeros meses por los investigadores del proyecto.
- La recogida de datos del parto (Anexo 3) fue realizada durante los 16 primeros meses por los investigadores del proyecto.
- Las encuestas de lactancia a los 3 y 6 meses de vida (Anexos 4 y 5) fueron llevadas a cabo vía telefónica por el investigador principal.
- La actualización de la base de datos se realizó de manera continua a lo largo del estudio.

Se establecieron 4 grupos según la vía del parto y la administración de oxitocina intraparto:

- Grupo pv-ox. Recién nacidos mediante parto vaginal sin administración de oxitocina sintética durante el trabajo de parto.
- Grupo pv+ox. Recién nacidos mediante parto vaginal con administración de oxitocina sintética durante el trabajo de parto.

- Grupo c+ox. Recién nacidos mediante cesárea con administración de oxitocina sintética durante el trabajo de parto.
- Grupo c-ox. Recién nacidos mediante cesárea sin administración de oxitocina (cesárea programada sin trabajo de parto previo).

Procedimiento de actuación

La forma de proceder durante el proceso de parto fue la siguiente: en los partos de inicio espontáneo no se empleó oxitocina exógena, salvo que la dinámica uterina fuera ineficaz. Cuando hubo indicación médica de finalizar la gestación, la inducción del parto se llevó a cabo mediante la infusión de oxitocina.

Para la administración de oxitocina se diluyó una ampolla de 10 UI (Syntocinon®, Sigma Tau) en 500 ml de suero salino al 0.9%. Se comenzó a un ritmo de infusión de 1 mUI/ minuto y se fue doblando la dosis cada 20 minutos hasta conseguir al menos 3 contracciones cada 10 minutos, siendo la dosis máxima recomendada 32 mUI/ minuto (método de Cardiff[6]).

En la tercera fase del parto, se llevó a cabo una conducta activa. Tras la salida del hombro anterior fetal, se administraron 5 UI de oxitocina a través del catéter venoso. Además, durante las 2 primeras horas del puerperio se mantuvo una perfusión de oxitocina a un ritmo de 2 UI/ hora.

En el caso de las cesáreas, se administraron 3 UI de oxitocina por el catéter venoso tras la extracción fetal y durante la primera hora del puerperio se infundieron 10 UI de oxitocina.

Cuando la paciente solicitó anestesia locorregional para controlar el dolor del parto, se procedió a la colocación de un catéter epidural y posterior infusión, previa firma del consentimiento informado correspondiente. Se empleó una perfusión de

levobupivacaína al 0.125% (Normon) asociada a fentanilo, o ropivacaína al 0.2% (Inibsa) asociada a fentanilo.

En los partos vaginales, cuando el recién nacido no necesitó maniobras de reanimación, se colocó sobre la madre, se secó, se identificó y se dejó en contacto precoz piel con piel durante 90 minutos.

Pasado este tiempo, se realizaron los cuidados de rutina (peso, talla, perímetro cefálico, profilaxis ocular y profilaxis antihemorrágica). Si el recién nacido aún no se había enganchado al pecho espontáneamente, se orientó a la diada madre/ hijo para favorecer el inicio de la LM.

En los nacimientos por cesárea, cuando las condiciones maternas y/o fetales lo permitieron, se realizó contacto precoz piel con piel durante el acto quirúrgico y posteriormente en la Unidad de Reanimación. En caso de no ser posible el contacto precoz piel con piel durante la intervención, se realizó una vez finalizada la cirugía en la Unidad de Reanimación (en los primeros 60 minutos de vida). En ningún caso, el recién nacido permaneció en un espacio diferente al de la madre.

Durante la estancia en el hospital, el personal de enfermería ofreció educación sanitaria en LM, favoreciendo el enganche del recién nacido y resolviendo las dudas propias del proceso de instauración.

Asimismo, tras el alta hospitalaria las madres pudieron realizar consultas sobre LM en un teléfono disponible las 24 horas del día.

Para registrar la dosis de oxitocina administrada durante el parto y el puerperio, un investigador del equipo cumplimentó un cuestionario de recogida de datos, y para registrar la duración de la LM se realizó llamada telefónica a los 3 y 6 meses de vida.

Se consideró LME a los 3 meses de vida cuando el lactante sólo había sido alimentado con leche materna, y a los 6 meses de vida cuando había sido alimentado con leche materna con o sin introducción de alimentación complementaria.

Se estimó pérdida en el seguimiento si tras cinco intentos de contacto telefónico, éste no se consiguió.

Variables de estudio e instrumentos de recogida de datos

Para estudiar la asociación de la administración de oxitocina sintética, la vía del parto, los factores sociodemográficos y otros factores del parto con la LM, se recogieron datos en diferentes tiempos:

- Cuaderno de recogida de datos del parto (Anexo3)
- Cuestionario de recogida de datos a los 3 meses de vida (Anexo 4).
- Cuestionario de recogida de datos a los 6 meses de vida (Anexo 5).

El cuestionario de recogida de datos del parto se cumplimentó de manera presencial en la Unidad de Trabajo de Parto y Recuperación. A los 3 y 6 meses, la recogida de datos se realizó por vía telefónica.

Método estadístico

El análisis descriptivo se realizó utilizando frecuencias absolutas y relativas para variables categóricas, y media (desviación estándar) o mediana (percentiles 25 a 75) para variables numéricas.

Las comparaciones de las características basales y entre los cuatro grupos se realizaron mediante el test de Kruskal-Wallis o el test de Chi cuadrado.

Para evaluar la asociación entre el grupo expuesto y el cese de la LME a lo largo del seguimiento, se realizó un análisis de ecuación de estimación generalizada (GEE)[51]. Este análisis considera las diferentes medidas a lo largo del tiempo para cada mujer y tiene en cuenta la correlación consiguiente. La variable dependiente fue el cese de la

LME en cada momento del seguimiento: al alta, 1 mes, 3 meses y 6 meses. Se aplicó una función enlace logit y la estructura de covarianza fue autorregresiva de orden 1. Primero se examinaron las asociaciones crudas que, cuando se encontraron, se ajustaron según posibles variables de confusión que, por criterios clínicos o estadísticos, ayudaron a evaluar si la asociación se debió a variables de confusión. El coeficiente de correlación de Pearson se utilizó para probar la correlación entre la dosis de oxitocina y la duración de la LME.

El análisis univariante se realizó con el test de Chi cuadrado o con el test exacto de Fisher para variables categóricas y la prueba U de Mann-Whitney para variables numéricas.

Para identificar los factores de riesgo asociados con el cese de la LME a los 3 y 6 meses posparto, se desarrollaron dos modelos de regresión logística multivariable. Todas las variables significativas en el análisis univariante se introdujeron en los modelos. Se siguió un procedimiento de eliminación no automático para llegar al modelo final según el principio de parsimonia (criterio para eliminar variables con $p> 0,05$). La bondad del ajuste se midió mediante calibración y discriminación. La calibración compara el número predicho de eventos con el número observado en grupos de individuos, mientras que la discriminación evalúa el grado en que el modelo distingue entre individuos en los que ocurre el evento y los que no. Se utilizó el test de Hosmer-Lemeshow[52] para evaluar la calibración y se usó el área bajo la curva ROC para evaluar la discriminación.

El nivel de significación estadística se estableció en 0,05. El análisis estadístico se realizó utilizando Stata / IC v.14.1. (StataCorp LP, College Station, TX)[53,54,55].

Aspectos éticos

La investigación se desarrolló de acuerdo con la declaración de Helsinki. El protocolo del estudio fue revisado y aprobado por el Comité Ético de Investigación Clínica del centro hospitalario (Anexo 1).

Antes de iniciar cualquier procedimiento se obtuvo el Consentimiento Informado de las participantes (Anexo 2).

RESULTADOS

Las características de la muestra están descritas en la tabla 1. El porcentaje de recién nacidos que inició LME fue del 90.4%. A los 3 meses de vida, el 64.4% de las madres mantenían LME, y a los 6 meses, el 31.4%.

Tabla 1. Características de la muestra, expresadas en valores absolutos (porcentajes), media (desviación estándar) o mediana (rango intercuartílico)

CARACTERÍSTICAS DE LA MUESTRA (n=529)	
Factores del parto	
Oxitocina sintética	294 (55.6%)
Cesárea Cesárea programada (presentación podálica, cesárea iterativa) Complicaciones durante el parto	106 (20%) 82 (77.4%) 24 (22.6%)
Analgesia locorregional	488 (92.2%)
EG RN (semanas), media (SD)	39.2 (1.1)
Peso RN (gramos), media (SD)	3,276 (400.2)
Factores sociodemográficos	
Estudios universitarios	356 (67.3%)
Primiparidad	227 (42.9%)
Educación prenatal	307(58%)
Edad materna (años), media (SD)	33.9 (4.3)
Nacionalidad española	465 (87.9%)
Pareja	524 (99%)
Sexo RN: mujer	283 (53.5%)
Test Apgar 5 minutos, mediana (IQ)	10 (10-10)
Uso de chupete	376 (71.9%)
Uso de chupete (edad RN, días), media (SD)	27.1 (22.2)
Asistencia grupo apoyo LM	131 (25%)
Incorporación laboral 3 meses 6 meses	 19 (3.6%) 294 (57.4%)
LME 3 meses 6 meses*	 337 (64.4%) 161 (31.4%)

EG: edad gestacional; RN: recién nacido

*Leche materna con o sin introducción de alimentación complementaria

Las características de la muestra para cada uno de los grupos de estudio están descritas en la tabla 2. Se observó que el grupo pv-ox recibió con menor frecuencia anestesia locorregional. Asimismo, se observaron diferencias entre los grupos en relación con la edad gestacional, la paridad y la educación prenatal.

Tabla 2. Características de la muestra para cada uno de los grupos, en valores absolutos (porcentajes), media (desviación estándar) o mediana (rango intercuartílico).

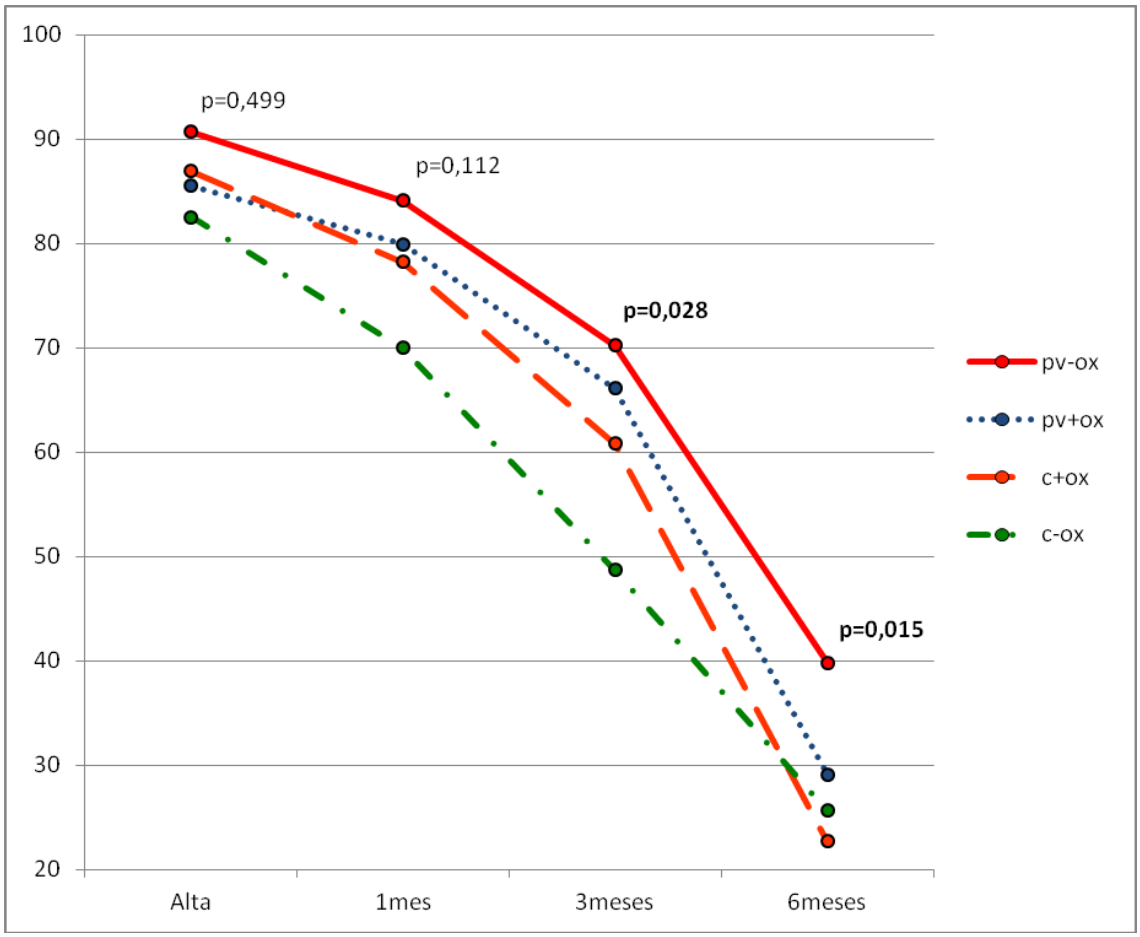
CARACTERÍSTICAS DE LA MUESTRA (n=529)					
	pv-ox (n=153)	**pv+ox** (n=270)	**c+ox** (n=24)	**c-ox** (n=82)	***p***
Factores del parto					
Anestesia locorregional	122 (79.7%)	263 (97.4%)	24 (100%)	82 (100%)	**<0.001**
EG RN (semanas), media (SD)	39.2 (0.9)	39.4 (1.2)	39.8 (1)	38.7 (0.9)	**<0.001**
Peso RN (gramos), media (SD)	3,238.5 (396.3)	3,290.9 (393.6)	3,271.4 (385.8)	3,300.8 (433.7)	0.687
Factores sociodemográficos					
Edad materna (años), media (SD)	33.4 (4.4)	33.9 (4.2)	35.1 (4)	34.5 (4.7)	0.070
Nacionalidad española	129 (84.3%)	246 (91.1%)	21 (87.5%)	69 (84.1%)	0.135
Estudios universitarios	103 (67.3%)	186 (68.9%)	14 (58.3%)	53 (64.6%)	0.694
Primiparidad	40 (26.1%)	138 (51.1%)	15 (62.5%)	34 (41.5%)	**<0.001**
Educación prenatal	78 (51%)	172 (63.7%)	17 (70.8%)	40 (48.8%)	**0.011**
Pareja	152 (99.3%)	269 (99.6%)	24 (100%)	79 (96.3%)	0.051
Sexo RN: mujer	76 (49.7%)	152 (56.3%)	10 (41.7%)	45 (54.9%)	0.367
Test Apgar 5 minutos, mediana (rango IQ)	10 (10-10)	10 (10-10)	10 (10-10)	10 (10-10)	0.384

pv: parto vaginal; ox: oxitocina; c: cesárea

EG: edad gestacional; RN: recién nacido

Al alta hospitalaria, la proporción de madres con LME fue del 90.7% en el grupo pv-ox, del 85.5% en el grupo pv+ox, del 87% en el grupo c+ox y del 82.5% en el grupo c-ox. Al mes, 3 y 6 meses, la proporción de LME disminuyó en todos los grupos (gráfico 1), siendo 84.1%, 70.2% y 39.9% respectivamente en el grupo pv-ox, 79.9%, 66.2% y 29.2% respectivamente en el grupo pv+ox, 78.2%, 60.9% y 22.7% respectivamente en el grupo c+ox y 70%, 48.7% y 25.6% respectivamente en el grupo c-ox, observándose diferencias estadísticamente significativas entre los grupos a los 3 y 6 meses de vida.

Gráfico 1. Porcentajes de LME por grupos en los diversos periodos de estudio



pv-ox: parto vaginal sin oxitocina; pv+ox: parto vaginal con oxitocina
c+ox: cesárea con oxitocina; c-ox: cesárea sin oxitocina

A partir de estos datos, se realizó un análisis de regresión GEE para determinar la asociación entre la administración de oxitocina sintética y la vía del parto y el cese de la LME al mes, 3 y 6 meses de vida (tabla 3). Tomando como referencia el grupo pv-ox, no se observaron diferencias a lo largo del tiempo de seguimiento en el cese de la LME en los grupos pv+ox y c+ox, pero sí en el grupo c-ox, observándose un riesgo mayor de abandono de la LME (OR 2.21, IC 95% 1.37-3.56).

Cuando se realizó el mismo análisis teniendo en cuenta aquellos factores de confusión que, según los resultados obtenidos en nuestra investigación[56], se asociaron con el cese de la LME (ausencia de estudios universitarios, uso de chupete, incorporación laboral, primiparidad y no asistencia a grupo de apoyo a la LM), se observó que el grupo c-ox tenía más riesgo de abandonar la LME a los 3 y 6 meses de vida que los otros tres grupos, OR 2.51 (IC 95% 1.53-4.12).

Tabla 3. Asociación entre vía del parto/administración de oxitocina y cese de LME en el periodo de seguimiento (1, 3 y 6 meses de vida)

	ANÁLISIS CRUDO		**ANÁLISIS AJUSTADO***	
Variable	**OR (CI 95%)**	***p***	**OR (CI 95%)**	***p***
pv-ox	Categoría de referencia	-	Categoría de referencia	-
pv+ox	1.43 (1.00-2.05)	**0.049**	1.35 (0.92-1.96)	0.119
c+ox	1.74 (0.80-3.76)	0.157	1.25 (0.56-2.80)	0.576
c-ox	2.21 (1.37-3.56)	**0.001**	2.51 (1.53-4.12)	**<0.001**

* ajustado según variables de confusión (ausencia de estudios universitarios, uso de chupete, incorporación laboral, primiparidad y no asistencia a grupo de apoyo a la LM)
pv: parto vaginal; ox: oxitocina; c: cesárea.

No se observó asociación entre la dosis de oxitocina administrada en el parto (media=2863.7; SD=3782 mUI) y el cese de la LME a los 3 meses (p=0.73; OR 1.01; 95% IC 0.94-1.07) y los 6 meses (p=0.55; OR 1.01; 95% IC 0.95-1.08). Tampoco se observó asociación entre la dosis de oxitocina administrada en el puerperio (media=12475.52; SD=6128.3 mU) y el cese de la LME a los 3 meses (p=0.06; OR 0.97; 95% IC 0.94-1.00) y los 6 meses (p=0.9; OR 0.99; 95% IC 0.96-1.02).

El análisis univariante de los factores del parto y sociodemográficos que pudieron influir en el cese de la LME a los 3 y 6 meses de vida se muestra en las tablas 4a y 4b. Se observó que el parto mediante cesárea, la ausencia de estudios universitarios, el uso de chupete, la no asistencia a grupo de apoyo a la LM y la incorporación laboral influyeron en el cese de la LME a los 3 meses de vida. La primiparidad, el uso de chupete y la incorporación laboral lo hicieron a los 6 meses de vida.

Tabla 4a. Análisis univariante de factores del parto y sociodemográficos que influyen en el cese de la LME a los 3 meses.

3 MESES DE VIDA (n=523)			
	LME **Valor absoluto (%)**	**LMM+LA** **Valor absoluto (%)**	***p***
Factores del parto			
Oxitocina sintética			0.479
Sí	192 (65.8)	100 (34.2)	
No	145 (62.8)	86 (37.2)	
Vía del parto			**0.002**
Vaginal	284 (67.6)	136 (32.4)	
Cesárea	53 (51.5)	50 (48.5)	
Analgesia locorregional			0.463
Sí	307 (63.7)	175 (36.3)	
No	28 (73.7)	10 (26.3)	
Factores sociodemográficos			
Nivel de estudios			**<0.001**
No universitarios	90 (53.6)	78 (46.4)	
Universitarios	247 (69.6)	108 (30.4)	
Paridad			0.619
Primiparidad	141 (63.2)	82 (36.8)	
Multiparidad	196 (65.3)	104 (34.7)	
Educación prenatal			0.478
Sí	201 (65.7)	105 (34.3)	
No	136 (62.7)	81 (37.3)	
Sexo del RN			0.146
Varón	148 (61.2)	94 (38.8)	
Mujer	189 (67.3)	92 (32.7)	
Uso del chupete			**<0.001**
Sí	217 (57.7)	159 (42.3)	
No	120 (81.6)	27 (18.4)	
Grupo de apoyo LM			**0.004**
Sí	98 (74.8)	33 (25.2)	
No	239 (61)	153 (39)	
Incorporación laboral			**0.010**
Sí	7 (36.8)	12 (63.2)	
No	330 (65.5)	174 (34.5)	

LMM: lactancia materna mixta; LA: lactancia artificial

Tabla 4b. Análisis univariante de factores del parto y sociodemográficos que influyen en el cese de la LME a los 6 meses.

6 MESES DE VIDA (n=512)			
	LME **Valor absoluto (%)**	**LMM+LA** **Valor absoluto (%)**	***p***
Factores del parto			
Oxitocina sintética Sí No	 82 (28.7) 79 (35)	 204 (71.3) 147 (65)	0.128
Vía del parto Vaginal Cesárea	 136 (33) 25 (25)	 276 (67) 75 (75)	0.118
Analgesia locorregional Sí No	 144 (30.6) 15 (39.5)	 327 (69.4) 23 (60.5)	0.220
Factores sociodemográficos			
Nivel de estudios No universitarios Universitarios	 44 (26.8) 117 (33.6)	 120 (73.2) 231 (66.4)	0.123
Paridad Primiparidad Multiparidad	 53 (24.5) 108 (36.5)	 163 (75.5) 188 (63.5)	**0.004**
Educación prenatal Sí No	 87 (28.9) 74 (35.1)	 214 (71.1) 137 (64.9)	0.139
Sexo del RN Varón Mujer	 70 (29.7) 91 (33)	 166 (70.3) 185 (67)	0.421
Uso del chupete Sí No	 89(24) 72 (51.1)	 282 (76) 69 (48.9)	**<0.001**
Grupo de apoyo LM Sí No	 47 (36.4) 114 (29.8)	 82 (63.6) 269 (70.2)	0.158
Incorporación laboral Sí No	 54(18.4) 107 (49.1)	 240 (81.6) 111 (50.9)	**<0.001**

LMM: lactancia materna mixta; LA: lactancia artificial

El modelo ajustado final se muestra en la tabla 5. La cesárea, la ausencia de estudios universitarios, la no asistencia a grupo de apoyo a la LM y el uso de chupete se asociaron con el cese de la LME a los 3 meses. La calibración y la discriminación fueron buenas, con un valor de *p* en el test de Hosmer-Lemeshow de 0.778 y un área bajo la curva de receptor-operador de 0.695.

Las variables asociadas con el cese de la LME a los 6 meses fueron primiparidad, incorporación laboral y uso de chupete. Todas estas variables permanecieron significativas en el modelo final (tabla 5). La calibración y la discriminación fueron buenas, con un valor de *p* en el test de Hosmer-Lemeshow de 0.998 y un área bajo la curva de receptor-operador de 0.748.

Tabla 5. Regresión logística multivariable de los factores asociados con el cese de la LME a los 3 y 6 meses de vida.

	ORs CRUDAS (CI 95%)	**ORs AJUSTADAS (CI 95%)**
Factores a los 3 meses		
Cesárea	1.98 (1.28-3.07)	2.31 (1.44-3.70)
Ausencia de estudios universitarios	1.98 (1.36-2.89)	2.01 (1.35-3.01)
Uso de chupete	3.25 (2.04-5.18)	3.85 (2.36-6.28)
No asistencia a grupo de apoyo a la LM	1.90 (1.21-2.96)	1.96 (1.22-3.12)
Incorporación laboral	3.25 (1.25-8.40)	---*
Factores a los 6 meses		
Primiparidad	1.76 (1.19-2.60)	1.61 (1.05-2.46)
Uso de chupete	3.30 (2.20-4.96)	3.49 (2.24-5.43)
Incorporación laboral	4.28 (2.88-6.37)	4.49 (2.96-6.83)

* La incorporación laboral no fue significativa cuando se incluyó en el modelo multivariable.

DISCUSIÓN

Según los resultados del presente estudio, la administración de oxitocina sintética durante el parto no se asocia con el cese de la LME en los diversos periodos de estudio. Estudiar la asociación entre la administración de oxitocina y el cese de la LME es una de las principales líneas de trabajo de nuestro grupo de investigación.

Se considera que existen dos barreras que evitan el paso potencial de oxitocina al cerebro del feto. Una es la barrera materno-placentaria, cuyas oxitocinasas parecen efectivas degradando la oxitocina. Algunos estudios sobre la difusión materno-fetal y feto-materna de oxitocina han encontrado que el transporte es mayor en dirección madre-feto, por lo tanto la oxitocina sintética administrada a la madre podría llegar a la circulación fetal[39]. Otra es la BHE del feto. Durante tiempo se pensó que la oxitocina no podía atravesar la BHE, pero la situación de estrés experimentada por madre e hijo durante el parto puede causar un aumento de la liberación de citoquinas (estrés oxidativo), de tal forma que la BHE sea más permeable de lo habitual[40]. En resumen, la oxitocina sintética administrada a la madre podría llegar al cerebro del feto[41].

En el primer estudio desarrollado por nuestro equipo observamos que las dosis de oxitocina que recibieron durante el parto las madres que no mantenían LME al mes y los 3 meses de vida fueron superiores a las dosis que recibieron aquellas que sí mantenían LME[46]. En una investigación posterior, no encontramos diferencias estadísticamente significativas entre la administración de oxitocina sintética intraparto y el inicio y duración de la LME[48] (Anexo 6).

En el presente estudio, se han analizado tanto las dosis de oxitocina administradas antes de la extracción fetal (dilatación y expulsivo) como las dosis de oxitocina administradas en las 2 primeras horas tras el parto (alumbramiento y primeras horas del puerperio

inmediato), no observándose asociación entre la dosis de oxitocina administrada en el parto y el cese de la LME a los 3 meses y 6 meses.

No obstante, se observó una tendencia a presentar mayores porcentajes de LME en el grupo pv-ox en ambos periodos (70.2% y 39.9% respectivamente), en comparación con los grupos que habían recibido oxitocina (66.2% y 29.2% en el grupo pv+ox; 60.9% y 22.7% en el grupo c+ox) (Anexo 7).

En un estudio retrospectivo llevado a cabo en España en 2014 con 316 mujeres (García-Fortea et al[43]), se observó que la administración de oxitocina durante el parto multiplicó por 2.29 el riesgo de no mantener LM a los 3 meses (resultado condicionado por la edad materna, siendo mayor para las madres menores de 27 años). La diferencia de hallazgos con respecto a nuestra investigación puede deberse a que se realizó en un hospital terciario sin acreditación IHAN. Asimismo, según una investigación realizada en Canadá por Gu et al[57] en 2016 (n=386), las madres que mantenían LME a los 2 meses de vida habían recibido menores dosis de oxitocina sintética durante el parto.

Con respecto a la administración de oxitocina en las 2 primeras horas tras el parto (alumbramiento y primeras horas del puerperio inmediato), no se ha encontrado asociación entre las dosis administradas y el cese de la LME a los 3 y 6 meses, si bien se observó una tendencia a la disminución de la LME a los 3 meses cuando las dosis fueron mayores (OR 0.97; 95% IC 0.94-1.00).

En esta línea, estudios previos relacionan la administración de oxitocina en el puerperio con el cese de la LM en diversos periodos. En 2014, Brown et al[58] realizaron una investigación retrospectiva con 288 mujeres y observaron que la administración de oxitocina profiláctica en el alumbramiento se relacionó con menores porcentajes de LM a las 2 y 6 semanas postparto. En 2009, Jordan et al[59] llevaron a cabo un estudio de

cohortes retrospectivo y también observaron menores proporciones de LM cuando se había administrado oxitocina para prevenir la hemorragia postparto.

En cuanto a la vía del parto y su posible asociación con el cese de la LME, nuestros resultados relacionan la cesárea electiva con el cese tanto a los 3 como a los 6 meses de vida, si bien el porcentaje de LME en este grupo ya era menor al alta hospitalaria. Así, a los 3 meses, el porcentaje de LME fue del 70.2% en el pv-ox y del 48.7% en la c-ox; a los 6 meses, fue del 39.9% en el pv-ox y del 25.6% en la c-ox (Anexo 7).

En el estudio prospectivo que Hobbs et al[60] realizaron en una región de Canadá en 2016, se incluyeron 3021 mujeres, y se analizó la relación entre la vía del parto y el inicio y duración de la LM, encontrando también asociación entre la cesárea electiva y el cese de la LM en los 4 primeros meses de vida. Asimismo, una investigación multicéntrica (n=9306) llevada a cabo por Zanardo et[61] al. en el norte de Italia de manera retrospectiva relacionó la cesárea electiva con el fracaso de la LM.

Cuando estudiamos la posible asociación entre la vía del parto y el cese de la LME, independientemente de la administración previa de oxitocina en el caso de cesárea, también observamos que el mantenimiento de la LME a los 3 meses fue menor cuando el parto tuvo lugar mediante cesárea en comparación con el parto vaginal (67.6% y 51.5% respectivamente). Estos datos coinciden con los resultados publicados por Oves Suárez et al[62], que relacionaron el parto vaginal con una mayor probabilidad de mantener LM a los 4 meses (83.3% frente a 16.7% para la cesárea). Adicionalmente, una revisión sistemática de Prior et al[63] (2012), que incluía 53 estudios y un meta-análisis con 48 estudios, concluyó que la cesárea se relacionaba con tasas más bajas de LM.

Los resultados obtenidos en la presente investigación también asocian otros factores del parto y factores sociodemográficos con el cese precoz de la LME, concretamente, el uso

de chupete, la ausencia de estudios universitarios, la no asistencia a grupo de apoyo a la LM, la primiparidad y la incorporación laboral (Anexo 8).

Estudios previos han relacionado la analgesia epidural con la duración de la LM. En una revisión sistemática llevada a cabo en 2015, se encontraron 23 artículos sobre estudios experimentales; la mitad de ellos mostraron una asociación negativa entre la analgesia epidural y la LM. Concluyeron que eran necesarias más investigaciones que relacionasen de manera objetiva las diferentes intervenciones del parto con el curso de la LM (French et al[64]). En nuestro estudio, si bien las tasas de LME a los 3 y 6 meses son mayores en el grupo de madres que no recibieron analgesia epidural, los resultados no son estadísticamente significativos.

Entre los factores sociodemográficos relacionados con el cese de la LM, el uso del chupete ha sido ampliamente investigado, y se ha asociado con una menor duración y exclusividad de la LM. Después de revisar la evidencia disponible, el Comité de LM de la Asociación Española de Pediatría recomienda evitar el chupete hasta que la LM está bien establecida, habitualmente hasta el primer mes de vida[65]. Según una revisión llevada a cabo por Jaafar et al[66], el uso de chupete una vez establecida la LM no afecta su prevalencia a los 4 meses de edad; sin embargo, concluye que no hay información suficiente acerca de los daños potenciales del chupete sobre el lactante. En el presente estudio, se encontró una asociación negativa entre el uso del chupete y la LME tanto a los 3 como a los 6 meses de vida. A los 3 meses, el 81.6% de los lactantes que no usaban chupete mantenían LME, mientras que si utilizaban chupete, continuaban el 57.7%. A los 6 meses, el 51.1% de los lactantes que no lo usaban mantenían LME, frente al 24% de los que lo utilizaban.

Otro factor a considerar es el nivel educativo de la madre. Así, según la investigación elaborada por Machado et al[67], las madres con menor nivel educativo eran las que más

frecuentemente abandonaban la LME a los 4 meses del parto. En 2013, Jessri et al[68] estudiaron predictores de LME y entre sus resultados destacaban que las madres con estudios universitarios y con hijos previos mantenían mayores tasas de LME a los 6 meses. La primiparidad puede por tanto tener una asociación negativa con la LM. Los resultados de nuestro trabajo relacionan la ausencia de estudios universitarios con el cese de la LME a los 3 meses de vida y la primiparidad con el cese de la LME a los 6 meses.

Con respecto a la asistencia a grupo de apoyo durante la LM, a los 3 meses de vida observamos que el porcentaje de LME era del 74.8% cuando las madres asistían y del 61% cuando no asistían a dichos grupos. En este sentido, Britton et al[69] revisaron 34 ensayos de 14 países, concluyendo que el apoyo ofrecido por profesionales podía ser efectivo para prolongar la LM, especialmente durante los 2 primeros meses. Añadieron que el apoyo presencial parecía ser más efectivo que el apoyo telefónico.

Por último, la incorporación laboral de la madre se ha relacionado con la duración y exclusividad de la LM. Bai et al[70] realizaron un estudio con 1738 madres y encontraron que sólo un tercio de ellas mantuvieron la LM a las 2 semanas de la incorporación laboral. En nuestra investigación, la incorporación laboral también se ha relacionado con el cese de la LME tanto a los 3 como a los 6 meses de vida, pero hay que considerar que a los 3 meses sólo se había incorporado al trabajo el 3.6% de la muestra, mientras que a los 6 meses lo había hecho el 57.4%.

LIMITACIONES

Nuestro estudio presenta algunas limitaciones que deben ser consideradas a la hora de interpretar los resultados. Existe un sesgo de selección, porque todas las participantes expresaron su deseo de dar LM antes del parto y sólo se incluyeron gestaciones únicas a término. Sin embargo, consideramos importante establecer la asociación entre la administración de oxitocina y la vía del parto y el cese precoz de la LME cuando las mujeres tenían deseo prenatal de dar LM, dado que se las suponía más motivadas para iniciar o mantener la LM. La investigación se desarrolló en un hospital con galardón IHAN. Estas particularidades pudieron minimizar el impacto de los factores analizados sobre el cese de la LME y reducir su validez externa.

Además, las madres recibieron información acerca de los objetivos del estudio, lo cual pudo condicionar el tipo de alimentación que ofrecieron a sus hijos a lo largo del periodo de seguimiento.

Otra limitación a tener en cuenta es que las participantes que asistieron a grupo de apoyo a la LM podrían estar más motivadas para mantener la LM, pudiendo ser la razón de una mayor duración de la LME en este grupo.

El porcentaje de mujeres que recibieron analgesia locorreginal varió en los diferentes grupos de estudio; de hecho, algunas investigaciones (French et al[64]) relacionan este método de control del dolor con peores resultados en LM. Además, la edad gestacional media en el momento del parto también fue diferente entre los grupos, pero no consideramos este dato clínicamente relevante.

También existe un sesgo de recuerdo que puede limitar la validez de la investigación, ya que la información sobre el tipo de alimentación se recogió de manera retrospectiva a los 3 y 6 meses del nacimiento. No obstante, existe evidencia acerca de que este tipo de cuestionarios tienen una elevada fiabilidad[71]. Las pérdidas de seguimiento podrían

limitar el estudio pero, dado que fueron mínimas (1.1% y 3.2% a los 3 y 6 meses respectivamente) y el tamaño muestral era adecuado, consideramos que no modificaron los resultados observados.

Otra limitación es que se consideró LME a los 6 meses la alimentación con leche materna con o sin introducción de alimentos complementarios. Asimismo, el mantenimiento de la LME a los 6 meses de vida podría verse afectado por la legislación vigente en España, donde el permiso retribuido por maternidad tiene una duración de 16 semanas.

Por último, puede haber otros factores relacionados con el cese precoz de la LME que no han sido analizados en la presente investigación, como la preexistencia de problemas de salud maternos, los estilos de vida, el nivel socioeconómico y la existencia de depresión puerperal entre otros. De hecho, en las llamadas telefónicas realizadas a los 3 y 6 meses, se invitó a las participantes a compartir las dificultades percibidas para mantener la LM y uno de los problemas más repetido fue la falta de atención hacia su estado emocional por parte de los profesionales, y la percepción de una atención centrada básicamente en las necesidades del niño.

CONCLUSIONES

- Primera. La administración de oxitocina durante el parto no se asocia con el cese de la LME en los diversos periodos de tiempo estudiados.
- Segunda. Las dosis de oxitocina administradas durante las 2 primeras horas tras el parto (alumbramiento y primeras horas del puerperio) tampoco se asocian con el cese de la LME, si bien la proporción de madres que mantuvieron LME a los 3 meses tendió a disminuir conforme aumentaron las dosis de oxitocina administradas.
- Tercera. El parto mediante cesárea programada (sin oxitocina) se asocia con el cese de la LME a los 3 y 6 meses de vida.
- Cuarta. En cuanto a la posible asociación de otros factores del parto y factores sociodemográficos con el cese precoz de la LME, nuestros resultados concluyen que la ausencia de estudios universitarios, el uso de chupete y la no asistencia a grupo de apoyo a la LM se asocian con el cese de la LME a los 3 meses de vida.
- Quinta. La primiparidad, el uso de chupete y la incorporación laboral se asocian con el cese de la LME a los 6 meses de vida.

A partir de estas conclusiones, y siguiendo las recomendaciones de la OMS[72], sería deseable ajustar la tasa de cesáreas a los casos en que estén oportunamente indicadas.
Asimismo, sería deseable diseñar estrategias para corregir los factores modificables así como promover los factores protectores, con el objetivo de mejorar el porcentaje de lactancias maternas exitosas hasta alcanzar las recomendaciones de la OMS.
Concretamente, sería beneficioso ofrecer una continuidad asistencial en asesoramiento sobre LM entre los diferentes niveles asistenciales (Atención Especializada y Atención Primaria). Para ello, sería necesario que todos los centros contasen con un número

adecuado de profesionales sanitarios específicamente formados en materia de LM que pudiesen desempeñar esta labor.

A nivel gubernamental, serían necesarias medidas que facilitasen el mantenimiento de la LME. La OMS recomienda la LME durante los 6 primeros meses de vida y en España, el periodo de descanso por maternidad solo tiene una duración de 16 semanas[73]. Con respecto al permiso de lactancia, éste se puede disfrutar hasta que el menor cumple 9 meses, y consiste únicamente en 1 hora diaria de ausencia del trabajo[74].

Para finalizar, consideramos que son necesarias más investigaciones que profundicen en la repercusión de la utilización de oxitocina sintética sobre la LM.

ABREVIATURAS

LME. Lactancia materna exclusiva

LM. Lactancia materna

OMS. Organización Mundial de la Salud

CRH. Hormona liberadora de corticotropina

DHEA-S. Sulfato de dehidroepiandrosterona

GCP. Gestación cronológicamente prolongada

RPM. Rotura prematura de membranas

SEGO. Sociedad Española de Ginecología y Obstetricia

CIR. Crecimiento intrauterino retardado

RPBF. Riesgo de pérdida del bienestar fetal

UCP2. Proteína de desacoplamiento mitocondrial 2

LA. Lactancia artificial

CID. Coagulación intravascular diseminada

Eje HPA. Eje hipotalámico-hipofisario-adrenal

BHE. Barrera hematoencefálica

IHAN. Iniciativa para la Humanización de la Asistencia al Nacimiento y la Lactancia

CEIC. Comité Ético de Investigación Clínica

pv. Parto vaginal

c. Cesárea

ox. Oxitocina

mUI. Miliunidades internacionales

UI. Unidades internacionales

BIBLIOGRAFÍA

1. Organización Mundial de la Salud. Alimentación del lactante y del niño pequeño; 2016 [consultado 13-09-2017]. Disponible en http://www.who.int/mediacentre/factsheets/fs342/es/
2. Ministerio de Sanidad y consumo. Estrategia de atención al parto normal en el Sistema Nacional de Salud. Madrid, 2008.
3. Hospital Universitario Puerta de Hierro. Protocolo de lactancia materna. Majadahonda, 2010. ISBN: 978-84-693-3024-1.
4. Organización Mundial de la Salud. Lactancia materna; 2016 [consultado 13-09-2017]. Disponible en http://www.who.int/topics/breastfeeding/es/
5. Asociación Española de Pediatría. Manual de Lactancia Materna. De la teoría a la práctica. Madrid: Editorial Médica Panamericana, 2009. ISBN: 978-84-7903-972-1.
6. Usandizaga JA, De la Fuente P. Obstetricia y Ginecología. Madrid: Marbán, 2011. ISBN: 978-84-7101-738-3.
7. SEGO. Protocolo de cesárea, 2015.
8. Observatorio de Resultados del Servicio Madrileño de Salud. Indicadores de Hospitales; 2016 [consultado 17-10-2017]. Disponible en http://observatorioresultados.sanidadmadrid.org/HospitalesDatosGeneralesTabla.aspx?ID=86
9. SEGO. Protocolo de parto vaginal tras cesárea, 2010.
10. Olza-Fernández I, Marín Gabriel MA, Gil-Sanchez A, Garcia-Segura LM, Arevalo MA. Neuroendocrinology of childbirth and mother-child attachment: the basis of an etiopathogenic model of perinatal neurobiological disorders. Front Neuroendocrino. 2014;35(4):459-72.

11. Simon-Areces J, Dietrich MO, Hermes G, Garcia-Segura, LM, Arevalo MA, Horvath TL. Ucp2 induced by natural birth regulates neuronal differentiation of the hippocampus and related adult behavior. PLoS One. 2012;7(8):e42911.
12. Bosch OJ, Neumann ID. Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. Horm Behav. 2012;61(3):293-303.
13. Nissen E, Lilja G, Widstrom AM, Uvnas-Moberg K. Elevation of oxytocin levels early post partum in women. Acta Obstet Gynecol Scand. 1995;74(7):530-533.
14. Winberg J. Mother and newborn baby: mutual regulation of physiology and behavior, a selective review. Dev Psychobiol. 2005;47(3):217-229.
15. Cassoni P, Marrocco T, Sapino A, Allia E, Bussolati G. Oxytocin synthesis within the normal and neoplastic breast: first evidence of a local peptide source. Int J Onco. 2006;28(5):1263-1268.
16. Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity, adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. Prog Brain Res. 2001;133:1-38.
17. Dewey KG. Maternal and fetal stress are associated with impaired lactogenesis in humans. J Nutr. 2001;131(11):3012S-5S.
18. Matthiesen AS, Ransjo-Arvidson AB, Nissen E, Uvnas-Moberg K. Postpartum maternal oxytocin release by newborns: effects of infant hand massage and sucking. Birth 2001;28(1):13-19.
19. Klaus M, Kennell J. Parent to infant bonding: setting the record straight. *J* Pediatr. 1983;102(4):575-576.

20. Bystrova K, Ivanova V, Edhborg M, Matthiesen AS, Ransjo-Arvidson AB, Mukhamedrakhimov R, et al. Early contact versus separation: effects on mother-infant interaction one year later. Birth 2009;36(2):97-109.
21. Carter CS. Developmental consequences of oxytocin. Physiol Behav. 2003; 79(3):383-397.
22. Pallás CR. Breastfeeding in Spain. A commitment by everyone. An Pediatr. 2015;83(6):365-6.
23. Rius JM, Ortuño J, Rivas C, Maravall M, Calzado MA, López A, et al. Factores asociados al abandono precoz de la lactancia materna en una región del este de España. An Pediatr. 2014;80:6-15.
24. Instituto Nacional de Estadística: Encuesta Nacional de Salud; 2013 [consultado 13-09-2017]. Disponible en http://www.ine.es/jaxi/Datos.htm?path=/t15/p419/a2011/p06/l0/&file=06154.px
25. Bagci AT, Eriksen KG, Sobko T, Wijnhoven TM, Breda J. Breastfeeding practices and policies in WHO European Region Member States. Public Health Nutr. 2016;19(4):753-64.
26. Dozier AM, Howard CR, Brownell EA, Wissler RN, Glantz JC, Ternullo SR, et al. Labor epidural anesthesia, obstetrics factors and breastfeeding cessation. Matern Child Health J. 2013;17:689-98.
27. Jonas K, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidson AB, Uvnäs-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. Breastfeed Med 2009;4:71-82.

28. Carter CS, Boone EM, Pournajafi-Nazarloo H, Bales KL. Consequences of early experiences and exposure to oxytocin and vasopressin are sexually dimorphic. Dev Neurosci. 2009;31(4):332-341.
29. Henry S, Richard-Yris MA, Tordjman S, Hausberger M. Neonatal handling affects durably bonding and social development. PLoS One. 2009;4(4):e5216.
30. Freeman RK, Nageotte M. A protocol for use of oxytocin. Am J Obstet Gynecol. 2007;197(5):445-446.
31. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009;200(1):35.e1-35.e6.
32. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica syntocinón, 2016 [consultado 04-10-2017]. Disponible en https://www.aemps.gob.es/cima/pdfs/es/ft/39393/39393_ft.pdf
33. Nissen E, Uvnas-Moberg K, Svensson K, Stock S, Widstrom AM, Winberg J. Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route. Early Hum Dev. 1996;5;45(1-2):103-118.
34. Reversi A, Cassoni P, Chini B. Oxytocin receptor signaling in myoepithelial and cancer cells. J Mammary Gland Biol Neoplasia. 2005;10(3):221-229.
35. Rossoni E, Feng J, Tirozzi B, Brown D, Leng G, Moos F. Emergent synchronous bursting of oxytocin neuronal network. PLoS Comput Biol. 2008;18;4(7):e1000123.
36. Febo M, Numan M, Ferris CF. Functional magnetic resonance imaging shows oxytocin activates brain regions associated with mother-pup bonding during suckling. J Neurosci. 2005;14;25(50):11637-11644.

37. Jonas W, Nissen E, Ransjo-Arvidson AB, Matthiesen AS, Uvnas-Moberg K. Influence of oxytocin or epidural analgesia on personality profile in breastfeeding women: a comparative study. Arch Womens Ment Health. 2008;11(5-6):335-345.
38. Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. Curr Opin Pharmacol. 2008;8(6):731-734.
39. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. J Matern Fetal Med. 1996;5(5):245-255.
40. Banks WA, Kastin AJ. Bidirectional passage of peptides across the blood-brain barrier. Prog Brain Res. 1992;91:139-148.
41. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders? A look at the literature. Med Hypotheses. 2004; 63(3):456-460.
42. Guerra GV, Cecatti JG, Souza JP, Faúndes A, Morais SS, Gülmezoglu AM, et al. Elective induction versus spontaneous labour in Latin America. Bull World Health Organ. 2011 Sep 1;89(9):657-65
43. Garcia-Fortea P, Gonzalez-Mesa E, Blasco M, Cazorla O, Delgado-Rios M, Gonzalez-Valenzuela MJ. Oxytocin administered during labor and breast-feeding: a retrospective cohort study. J Matern Fetal Neonatal Med. 2014;27(15):1598-1603.
44. Bai DL, Wu KM, Tarrant M. Association between intrapartum interventions and breastfeeding duration. J Midwifery Womens Health. 2013;58(1):25-32.
45. Olza I, Marín MA, Malalana A, Fernández-Cañadas A, López F, Costarelli V. Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. Acta Paediatr. 2012;101(7):749-754

46. Marín MA, Olza I, Malalana A, Martínez B, Fernández-Cañadas A. Influencia de la oxitocina administrada durante el parto en el mantenimiento de la lactancia materna. Estudio Preliminar. Acta Pediatr Esp. 2012;70(11):269-71.
47. Marín MA, Olza I, Malalana A, González C, Costarelli V, Millán I, et al. Intrapartum synthetic oxytocin reduce the expression of primitive reflexes associated with breastfeeding. Breastfeed Med. 2015;10(4):209-13.
48. Fernández-Cañadas A, Marín MA, Olza I, Martínez B, Durán M, Malalana A, et al. The relationship of the administration of intrapartum synthetic oxytocin and breastfeeding initiation and duration rates. Breastfeed Med. 2017;12:98-102.
49. Zakarija-Grkovic I, Segvic O, Vuckovic Vukusic A, , Lozancic T, Bozinovic T, Cuze A, et al. Predictors of suboptimal breastfeeding: an opportunity for public health interventions. Eur J Public Health. 2016;26:282-9.
50. Bonet M, Marchand L, Kaminski M, Fohran A, Betoko A, Charles MA, et al. Breastfeeding duration, social and occupational characteristics of mothers in the French 'EDEN mother-child' cohort. Matern Child Health J. 2013;17:714-22.
51. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol. 2003;157(4):364-75.
52. Hosmer, David W.; Lemeshow, Stanley (2013). Applied Logistic Regression. New York: Wiley. ISBN 978-0-470-58247-3.
53. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: Developing a prognostic model. BMJ. 2009;338:b604.
54. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009;338:b605.

55. Harrell FE Jr. Regression modeling strategies with applications to linear models, logistic regression, and survival analysis. New York: Springer, 2001.
56. Fernández-Cañadas A, Durán M, Hernández AB, Muriel C, Martínez B, Oscoz A, et al. A comparison of factors associated with cessation of exclusive breastfeeding at 3 and 6 months. Breastfeed Med. 2017;12(7):430-435.
57. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, et al. Intrapartum synthetic oxytocin and its effects on maternal well-being al 2 months postpartum. Birth. 2016;43:28-35.
58. Brown A, Jordan S. Active management of the third stage of labor may reduce breastfeeding duration due to pain and physical complications. Breastfeed Med. 2014;9:494-502.
59. Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Association of drugs routinely given in labour with breastfeeding at 48 hours: analysis of de Cardiff Births Survey. BJOG. 2009;116:1622-9.
60. Hobbs AJ, Mannion CA, McDonald SW, Brockway M, Tough SC. The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. BMC Pregnancy and Chidbirth. 2016;16:90.
61. Zanardo V, Pigozzo A, Wainer G, Marchesoni D, Gasparoni A, Di Fabio S, et al. Early lactation failure and formula adoption after elective caesarean delivery: cohort study. Arch Dis Child Fetal Neonatal Ed. 2013;98:F37-41.
62. Oves B, Escartín L, Samper MP, Cuadrón L, Alvarez ML, Lasarte JJ, et al. Inmigración y factores asociados con la lactancia materna. Estudio CALINA. An Pediatr. 2014;81:32-38.

63. Prior E, Santhakumaran S, Gale C, Philipps LH, Modi N, Hyde MJ. Breastfeeding after cesarean delivery: a systematic review and meta-analysis of world literature. Am J Clin Nutr. 2012;95:1113-35.
64. French CA, Cong X, Chung KS. Labor epidural analgesia and breastfeeding: a systematic review. J Hum Lact. 2016;32:507-20.
65. Lozano MJ, Pallás CR, Hernández MT, Aguayo J, Arena J, Ares S, et al. Uso del chupete y lactancia materna. An Pediatr. 2011;74:271.e1-271.e5.
66. Jaafar SH, Jahanfar S, Angolkarm, Ho JJ. Effect of restricted pacifier use in breastfeeding term infants for increasing duration of breastfeeding (Review). Cochrane Database Syst Rev. 2012 Jul 11;(7):CD007202.
67. Machado MC, Assis KF, Oliveira FC, Ribeiro AQ, Araújo RM, Cury AF, et al. Determinants of the exclusive breastfeeding abandonment: psychosocial factors. Rev Saúde Pública. 2014;48:985-994.
68. Jessri M, Farmer AP, Maximova K, Willows ND, Bell RC; APrON Study Team. Predictors of exclusive breastfeeding: observations from the Alberta pregnancy outcomes and nutrition (APrON) study. BMC Pediatrics. 2013;13:77.
69. Britton C, McCormick FM, Renfrew Mj, Wade A, King SE. Support for breastfeeding mothers (Review). Cochrane Database Syst Rev. 2007 Jan 24;(1):CD001141.
70. Bai DL, Fong DY, Tarrant M. Factors associated with breastfeeding duration and exclusivity in mothers returning to paid employment postpartum. Matern Child Health J. 2015;19:990-9.
71. Natland ST, Andersen LF, Nilsen TI, Forsmo S, Jacobsen GW. Maternal recall of breastfeeding duration twenty years after delivery. BMC Med Res Methodol. 2012;12:179.

72. Organización Mundial de la Salud. Declaración de la OMS sobre tasas de cesárea; 2015 [consultado 22-06-2017]. Disponible en http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/cs-statement/es/

73. Ministerio de Empleo y Seguridad Social. Prestación de Maternidad; 2017 [consultado 29-09-2017]. Disponible en http://www.seg-social.es/Internet_1/Masinformacion/TramitesyGestiones/PrestaciondeMaterni43344/index.htm

74. Ministerio de Sanidad, Servicios Sociales e Igualdad. La lactancia; 2017 [consultado 29-09-2017]. Disponible en http://www.inmujer.gob.es/conoceDerechos/preguntas/lactancia.htm#duracionPermiso

ANEXO 1. APROBACIÓN CEIC

ANEXO 2. CONSENTIMIENTO INFORMADO

HOJA DE INFORMACIÓN PARA LA PARTICIPANTE

Titulo del proyecto: Administración de oxitocina y vía del parto: posible influencia en la lactancia materna.

Investigadores principales: Aurora Fernández Cañadas Morillo. (Matrona. Servicio de Obstetricia y Ginecología. HUPH). Miguel Ángel Marín Gabriel (Neonatólogo. Servicio de Pediatría. HUPH).

Investigadores colaboradores: Modesto Durán Duque, Ana Belén Hernández López y Cristina Muriel Miguel (Matronas. Servicio de Obstetricia y Ginecología. HUPH). Ana Oscoz Prim y Pilar Pérez Riveiro (Enfermeras. Servicio de Obstetricia y Ginecología. HUPH).

Teléfono de contacto: para contactar con los investigadores, puede llamar al Hospital Puerta de Hierro (91. 191.60.00) y solicitar que le pongan en comunicación con el área de Paritorio.

Centro de referencia: Hospital Universitario Puerta de Hierro de Majadahonda.

Introducción

Los Servicios de Obstetricia y Neonatología estamos realizando un estudio para valorar ciertos factores que pueden influir en el inicio y mantenimiento de la lactancia materna.

Para ello se estudiarán cuatro grupos de madres y recién nacidos: 1) las que han tenido un parto vaginal sin administración de oxitocina; 2) las que han tenido un parto vaginal inducido con oxitocina; 3) aquellas que han tenido una cesárea con trabajo de parto previo; y 4) aquellas que han tenido una cesárea programada sin trabajo de parto previo.

Se le propone participar en este estudio porque usted va a tener a su hija/o en este hospital y pertenece a alguno de los grupos citados. El estudio ha sido aprobado por el Comité Ético de Investigación Clínica del Hospital Universitario Puerta de Hierro (P.I. 11/15).

Nuestra intención es que usted reciba la información correcta y suficiente para que pueda evaluar y juzgar si quiere o no participar en este estudio. Para ello lea esta hoja informativa con atención y nosotros le aclararemos las dudas que le puedan surgir después de la explicación.

Participación voluntaria

Debe saber que su participación y la de su hijo en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento.

En ningún caso, su decisión afectará a la atención y cuidados que reciba por parte de los profesionales de la salud.

Descripción general del estudio

Se trata de un estudio descriptivo prospectivo del que formarán parte cuatro grupos de parejas madre-hijo (grupo 1: madres que han tenido un parto vaginal y no han recibido oxitocina; grupo 2: madres que han tenido un parto vaginal y han recibido oxitocina; grupo 3: madres que han tenido una cesárea con trabajo de parto previo y grupo 4: madres que han tenido una cesárea programada).

Tras la firma de este documento de consentimiento informado, se recogerán algunos datos relacionados con sus antecedentes médicos y con el proceso del parto. También se recogerán ciertos datos de salud relacionados con su hijo (peso, edad gestacional, test de Apgar).

Por último, nos pondremos en contacto con usted vía telefónica para realizarle algunas preguntas en relación con la alimentación de su hijo a los 3 meses y a los 6 meses del nacimiento.

Beneficios y riesgos derivados de su participación en el estudio

No se espera que ni usted ni su hijo se beneficien directamente de los resultados de esta investigación. Sin embargo, poder aumentar el conocimiento sobre los factores que influyen en el inicio y mantenimiento de la lactancia materna permitirá introducir cambios en la asistencia que favorezcan este tipo de alimentación.

No existe ningún riesgo adicional por su participación en este estudio, sólo se van a recoger datos relacionados con el parto y la lactancia materna para su posterior análisis.

Confidencialidad

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal. De acuerdo a lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a los investigadores del proyecto.

Los datos recogidos para el estudio estarán identificados mediante un código y solo el equipo investigador podrá conocer la relación entre el código y la identidad del paciente.

CONSENTIMIENTO INFORMADO

Titulo del proyecto: Administración de oxitocina y vía del parto: posible influencia en la lactancia materna.

Yo (nombre y apellidos)……..
con DNI……..

- He leído la hoja de información que se me ha entregado.
- He podido hacer preguntas sobre el estudio.
- He recibido suficiente información sobre el estudio.

He hablado con (nombre del investigador) ……..

- Comprendo que mi participación es voluntaria.
- Comprendo que puedo retirarme del estudio:

  1º Voluntariamente

  2º Sin tener que dar explicaciones.

  3º Sin que esto repercuta en mis cuidados médicos.

Por consiguiente:

Presto libremente mi conformidad para participar en el estudio y doy mi consentimiento para el acceso y utilización de mis datos en las condiciones detalladas en la hoja de información.

FIRMA DE LA PARTICIPANTE **FIRMA DEL INVESTIGADOR**

Fecha: **Fech**a:

ANEXO 3. CUADERNO DE RECOGIDA DE DATOS DEL PARTO

CUADERNO DE RECOGIDA DE DATOS DEL PARTO

IDENTIFICACIÓN

- Código de identificación de la participante: _____
- Fecha del parto: _____
- Grupo de estudio: 1 2 3 4

VARIABLES MATERNAS

1) Edad: _____ años

2) Nivel de estudios:

- Sin estudios □
- Primarios □
- Secundarios □
- Universitarios □

3) Estado civil:

- Con pareja □
- Sin pareja □

4) Antecedentes médicos: _____

_____

5) Paridad: G A P

6) Edad gestacional: _____

7) Asistencia durante el embarazo al programa de Educación Maternal de Atención Primaria:

- Si □
- No □

8) Inicio del parto:

- Espontáneo □
- Inducción □
    - Prostaglandinas □
    - Oxitocina □
- Cesárea programada □

9) Ruptura de membranas:

- Espontánea □
- Artificial □

10) Fecha y hora de ruptura de membranas: _____

11) Tipo de parto:

- Grupo 1. Parto vaginal con admón de oxitocina durante el trabajo de parto □
  (eutócico □; ventosa □; espátulas □; fórceps □)
- Grupo 2. Cesárea con admón de oxitocina durante el trabajo de parto □
  (contacto precoz piel con piel durante el acto quirúrgico: sí □; no □)
- Grupo 3. Parto vaginal sin admón de oxitocina durante el trabajo de parto □
  (eutócico □; ventosa □; espátulas □; fórceps □)
- Grupo 4. Cesárea programada □
  (contacto precoz piel con piel durante el acto quirúrgico: sí □; no □)

12) Fecha y hora del parto: _____

13) Analgesia epidural:

- Sí □
- No □

14) Administración de antibioterapia durante el parto:

- Sí □
- No □

15) Administración de oxitocina durante el parto:

- Sí □
- No □

16) Dosis de oxitocina acumulada en el momento del parto: _____mU

17) Tipo de alumbramiento:

- Dirigido □
- Espontáneo □

18) Dosis de oxitocina administrada en el puerperio: _____mU

19) Administración de carbetocina (Duratobal) en el puerperio:

- Sí □
- No □

20) Sexo del recién nacido:

- Varón □
- Mujer □

21) Peso del recién nacido (g) _____

22) Test de Apgar del recién nacido a los 5 minutos de vida _____

23) Tipo de reanimación:

- No precisa (rea 0) □
- Aspiración de secreciones (rea 1) □
- Ventilación con presión positiva (rea 3) □
- Intubación (rea 4) □
- Administración de drogas (rea 5) □

24) Ingreso del recién nacido en la Unidad Neonatal:

- Sí □
- No □

ANEXO 4. CUESTIONARIO DE RECOGIDA DE DATOS A LOS 3 MESES DE VIDA

CUESTINARIO DE RECOGIDA DE DATOS A LOS 3 MESES DE VIDA

IDENTIFICACIÓN

- Código de identificación de la participante: _____
- Fecha del parto: _____
- Cuestionario:
  - Respondido □
  - No desea responder □
  - No se consigue contacto □ Fecha_____ Fecha _____ Fecha _____

CUESTIONARIO LACTANCIA MATERNA. 3 MESES DE VIDA.

1) Tipo de lactancia durante la estancia en el Hospital:
   - LM completa □
   - LM mixta □
   - LA □
2) Administración de suplementos durante la estancia hospitalaria:
   - Sí □
   - No □
3) Motivo del suplemento:
   - Pérdida de peso/deshidratación □
   - Hipoglucemia □
   - Deseo de los padres □
   - No existe realmente motivo de indicación □
   - Otros_____ □
4) Tipo de lactancia al alta:
   - LM completa □
   - LM mixta □
   - LA □

5) Uso de chupete:

- A partir del _____día de vida □
- No usa chupete □

6) ¿Se ha puesto en contacto con algún Grupo de Apoyo de la LM?

- Sí □
- No □

7) Tipo de lactancia al mes:

- LM completa □
- LM mixta □
- LA □

8) Tipo de lactancia a los 3 meses:

- LM completa □
- LM mixta □
- LA □

9) Duración LM exclusiva_____ días.

10) Duración total de LM (si se ha destetado) _____ días.

11) Si se ha destetado ya, ¿puede describir como fue el destete? _____

_____

12) ¿Se ha incorporado a su trabajo?

- Sí □ ¿Cuándo? _____ (edad del RN)
- No □

13) Durante el embarazo, ¿qué tipo de alimentación tenía pensado ofrecer a su recién nacido?

_____

_____

14) ¿Desea hacer algún comentario? (comentar dificultades percibidas con la lactancia)

_____

_____

ANEXO 5. CUESTIONARIO DE RECOGIDA DE DATOS A LOS 6 MESES DE VIDA

CUESTIONARIO DE RECOGIDA DE DATOS A LOS 6 MESES DE VIDA

IDENTIFICACIÓN

- Código de identificación de la participante: _____
- Fecha del parto: _____
- Cuestionario:
  - Respondido □
  - No desea responder □
  - No se consigue contacto □ Fecha _____ Fecha _____ Fecha _____

CUESTIONARIO LACTANCIA MATERNA. 6 MESES DE VIDA.

1) Tipo de lactancia a los 3 meses:

- LM completa □
- LM mixta □
- LA □

2) Tipo de lactancia a los 6 meses:

- LM completa □
- LM mixta □
- LA □

3) Duración LM exclusiva _____ días.

4) Duración total de LM (si se ha destetado) _____ días.

5) Si se ha destetado ya, ¿puede describir como fue el destete? _____

_____

6) ¿En qué momento introdujo leche artificial/ alimentación complementaria?

- Leche artificial (edad del RN) _____
- Alimentación complementaria (edad del RN) _____

7) Si sigue tomando leche materna: ¿Cuántas tomas hace al día? _____

8) ¿Dónde duerme el bebé?

- En cuna en habitación diferente de la madre/padres □
- En cuna en la misma habitación que la madre/padres □
- En la cama de la madre/padres (colecho) □

9) ¿Se ha incorporado a su trabajo?

- Sí □ ¿Cuándo? _____ (edad del RN)
- No □

10) ¿Va a la guardería?

- Sí □
- No □

11) En caso afirmativo:

- ¿Desde qué edad va a la guardería? _____
- Número de horas en la actualidad _____

12) ¿Desea hacer algún comentario sobre su experiencia con la lactancia? (comentar dificultades percibidas) _____

_____

13) ¿Tiene más hijos? (rodear número): 1 2 3 4 5 o más

14) ¿Cuánto tiempo les amamantó?

- 1º duración lactancia:
- 2º duración lactancia:
- 3º duración lactancia:
- 4º duración lactancia:
- 5º duración lactancia:

ANEXO 6. Artículo revista Breastfeeding Medicine. “The relationship of the administration of intrapartum synthetic oxytocin and breastfeeding initiation and duration rates”.

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Clinical Research

The Relationship of the Administration of Intrapartum Synthetic Oxytocin and Breastfeeding Initiation and Duration Rates

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Abstract

Aim: The consequences that intrapartum administration of hormones can have on breastfeeding are unclear. The aim of the study is to determine if synthetic intrapartum oxytocin, used routinely for induction/stimulation, has a relationship to initiation/duration of breastfeeding.
Patients and Methods: We conducted a cohort study that was carried out in a tertiary university hospital distinguished by WHO-UNICEF as a BFHI (Baby-Friendly Hospital Initiative). A group of 53 mother and newborn dyads who had been exposed to intrapartum synthetic oxytocin were compared with 45 nonexposed dyads. A breastfeeding questionnaire was administered by a midwife blind to patient group through phone calls 3 and 6 months after delivery.
Results: No statistically significant differences were observed between the two groups in the rates of mothers exclusively breastfeeding (EBF) or nonexclusively breastfeeding. The percentage of those who were EBF when discharged was 97.3% in the oxytocin-nonexposed group and 87.1% in the oxytocin-exposed group ($p = 0.14$). At 3 months, the group rates of exclusive breastfeeding were 72.5% in the nonoxytocin-exposed group versus 65.9% in the oxytocin-exposed group ($p = 0.71$). At 6 months, rates of breastfeeding were 31.4% versus 27.9% ($p = 0.53$) in the oxytocin-nonexposed and oxytocin-exposed groups, respectively.
Conclusions: In this study, no statistically significant effect of intrapartum synthetic oxytocin administration was observed pertaining to the initiation or duration of breastfeeding.

Keywords: breastfeeding, synthetic oxytocin, intrapartum, newborn

Introduction

EVIDENCE SAYS THAT maternal breastfeeding is beneficial. Breastfeeding is associated with a decrease in the risk of diabetes and other autoimmune disorders, protection against infectious illnesses, improvement of intelligence quotient, and decrease in mortality among other benefits.[1–3]

To obtain these beneficial effects, maintenance of breastfeeding is an important issue. Several factors can impact the number of months of breastfeeding, such as prenatal education, pacifier use, or sharing the room with the newborn.[4] In addition, several interventions during birth can have an effect on breastfeeding. Among the most common interventions are cesarean surgeries[5] and exposure to different drugs used to augment contractions or to decrease pain. The results of interventions such as epidural analgesia on breastfeeding duration are unclear.[6,7]

During labor, it is common to administer synthetic oxytocin to obtain effective uterine activity, especially in nulliparous women.[8]

Some authors consider exogenous oxytocin to be the drug that is most associated with preventable or avoidable adverse effects in childbirth.[9] Oxytocin administration is one of the single most frequently used induction method. The use of the hormone without any medical or obstetric indication is increasing in developed countries. For example, in a study in Italy in 1992, the drug was used in 17.5% of induced deliveries, while in a more recent study in Latin America, it was used in 65.9% of induced deliveries.[10,11] Synthetic oxytocin during delivery is so widespread that there is a tendency to assume that its effects are well known. At first, it was assumed that the use was safe for fetuses because the placental barrier and blood–brain barrier were thought to provide natural protection. We did not find studies supporting these assumptions. Malek et al.[12] studied the human

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placental transport of oxytocin and found that oxytocin administered to the mother could pass to the fetal circulatory system. Wahl showed that permeability of the blood–brain barrier can increase during stressful situations because of the liberation of proinflammatory cytokines.[13] Labor is a high stress situation for both the mother and child, and could facilitate passing synthetic oxytocin across the placental barrier to the baby's brain.

Ounsted et al.[14] were among the first researchers to describe how different strategies in labor induction in humans can affect breastfeeding. They observed in a group of 184 primiparous women that newborns delivered by natural childbirth received maternal breastfeeding more frequently, both during hospital intake and at discharge, compared with newborns whose labors were induced with oxytocin. In contrast with these findings, Out et al.[15] studied 185 mothers and affirmed that the administration of oxytocin for induction of labor does not influence the establishment of breastfeeding.

In a secondary analysis study in 2011, Guerra et al.[11] analyzed data from 37,444 pregnancies. They found that delayed initiation of breastfeeding was more common among women who had an elective induction of labor. However, this retrospective study did not examine the possible effects that delivery induction could have on breastfeeding duration. Likewise, a retrospective study in Spain comparing 189 neonates exposed to oxytocin during labor with 127 unexposed neonates found that the drug was linked to greater difficulty in the initiation and maintenance of breastfeeding.[16]

In contrast to these findings, Bai et al.[17] performed a multicenter prospective study in Hong Kong, observing that each labor induction, pain reliever opioid use, or cesarean section did not influence maternal breastfeeding. They did, however, indicate that multiple intrapartum interventions significantly increased the likelihood of breastfeeding cessation.

In a previous study, we found that intrapartum oxytocin administration might inhibit the expression of several primitive neonatal reflexes associated with breastfeeding.[18] The aim of the study is to determine if synthetic intrapartum oxytocin has a relationship to initiation/duration of breastfeeding.

Patients and Methods

A prospective, observational cohort study was conducted at a tertiary hospital that holds the Baby-Friendly Hospital Initiative (BFHI) designation of the WHO-UNICEF. The study was reviewed and approved by the Review Board of the Hospital Universitario Puerta de Hierro, Majadahonda (Madrid). During intake, hospital midwives explained the study opportunity to all mothers who fulfilled inclusion criteria before delivery in the hospital. Mothers provided informed consent to participate. The sample comprised two groups: the exposed group, consisting of the mother–child dyads, in which oxytocin was administered during labor, and the comparison group, comprising the mother–child dyads, in which oxytocin was not administered. Inclusion criteria were healthy single-birth newborns who were delivered vaginally at full-term with an Apgar score of at least seven at 5 minutes. In addition, mothers must have expressed a desire to breastfeed during pregnancy. Exclusion criteria were preterm infants; fetal chromosomal abnormalities diagnosed in utero; maternal admission in Intensive Care Unit; newborn Neonatal Intensive Care Unit admission in the 48 hours following delivery; lack of maternal desire to breastfeed expressed before delivery; language difficulties; and caesarean sections. Families did not receive financial compensation for their enrollment. Information such as the newborn's gestational age, sex, weight, Apgar score, and the mother's educational level, previous pregnancies, and marital status was collected, as well as information regarding the use of instruments during delivery (such as forceps).

Oxytocin induction/stimulation in the exposed group was performed by obstetrical indication (not electively) according to Bishop test under the Cardiff method: preparation of 10 U of oxytocin (Syntocinon®; Defiante Pharmaceutics) in 500 mL of saline solution at 0.9%. Administration began with 2 mUI and was doubled every 15 minutes until at least three contractions in 10 minutes appeared, with a maximum allowance of 40 mUI. The final oxytocin dose was recorded by midwives assisting with the labor process. The most common indications were overdue and premature rupture of membranes. All mothers received oxytocin during the third stage of labor as recommended to prevent postpartum hemorrhage.

For epidural anesthesia, mothers received levobupivacaine at 0.125% (Chirocane®; Abbott) combined with fentanyl or ropivacaine at 0.2% (Naropin® Polybag®; AstraZeneca) combined with fentanyl.

Infants were considered exclusively breastfed (EBF) if they received no other liquids or breast milk substitutes (other than vitamins or medications). They were considered partially breastfed (PBF) if they were supplemented with infant formula and/or other breast milk substitutes and were considered formula fed if they had not received any amount of breastfeeding.

After discharge, a questionnaire was administered blindly at 3 and 6 months by phone. Data for the 1-month follow-up were collected during the 3-month call. If participants were unable to be reached after three calls on three different days, they were considered lost to follow-up.

Analyses were performed using SPSS version 14.[19] Descriptive statistics were used to describe the sample characteristics and the duration of breastfeeding. Results are expressed in mean ± standard deviation or median and interquartile range. Qualitative variables are expressed as absolute frequencies and percentages. Shapiro–Wilk test was conducted to confirm the normal distribution hypothesis. The comparisons between groups have been performed with Student's t test for independent samples and the Mann–Whitney nonparametric test. For qualitative variables, we used χ^2 and Yates and Fisher corrections if necessary. All p-values were two-sided and values of 0.05 or less were considered to indicate statistical significance.

This study is a secondary objective of a project aimed to evaluate the effects of oxytocin administered during labor on primitive neonatal reflexes. It was approved by the local ethics committee and is registered in ClinicalTrials.gov under identification number NCT01891201. It was funded by the Health Research Fund, FIS No. PI10/00791.

Results

We recruited 57 dyads for the oxytocin-exposed group and 48 for the nonexposed group. After initial inclusion in the study, four mother–child dyads (7.5%) in the exposed group were excluded (two for revocation of informed consent and two for lack of data regarding the administered oxytocin dose). In the nonexposed group, three dyads (6.6%) were excluded: one newborn had a broken collarbone, another was admitted to receive phototherapy, and the third had a gastric lavage. The final sample was 53 dyads in the exposed group and 45 in the nonexposed group.

Table 1. Maternal and Neonatal Sample Descriptive Data

	Nonexposed group (n = *45*)	*Oxytocin-exposed group* (n = *53*)	p
Maternal education			0.98
Primary	2.4%	2.1%	
Secondary	34.1%	33.3%	
University	63.4%	64.6%	
Previous gestation	78.6%	55.1%	0.01
Previous children	73.8%	40.8%	0.002
Gestational age (weeks)[a]	39.2 ± 1.1	39.7 ± 1	0.06
Newborn weight (grams)[a]	3,245.3 ± 472	3,323.8 ± 375.4	0.39
Sex of the newborn (% female)	52.4%	49%	0.16
Use of pacifier	54.1%	73.7%	0.07
Maternal return to work at 6 months	51.4%	51.2%	0.98
Age of children at maternal return to work[a]	130.8 ± 34.8	144.8 ± 35.3	0.21
Babies day care at 6 months	20%	27.9%	0.45
Child age at day care onset[a]	137.1 ± 18.2	130.8 ± 60.1	0.79

[a]Indicates mean ± standard deviation.

For the 3-month questionnaire, we were able to contact 40 subjects (75.5%) in the oxytocin-exposed group and 44 (97.7%) in the nonoxytocin-exposed group. For the 6-month evaluation, we collected data from 43 participants (81.1%) in the oxytocin-exposed group and 35 (77.7%) in the nonexposed group. We were not able to contact the 14% of the original sample at any time point.

As shown in Table 1, we did not find statistically significant differences between the two groups in several maternal and neonatal characteristics; nonetheless, the nonexposed group included a higher percentage of women with previous pregnancies ($p = 0.01$) and more women in this group had previous children ($p < 0.01$). All mothers with previous children had a previous breastfeeding experience. The nonoxytocin-exposed group introduced pacifiers earlier (16.2 ± 12.2 days) than the oxytocin-exposed group (34.8 ± 32.7 days) ($p = 0.02$).

Characteristics of labor are shown in Table 2. All deliveries in the nonoxytocin-exposed group were conducted without instruments, while in the exposed group, 22.4% involved instruments ($p < 0.01$). The oxytocin-exposed group received epidural anesthesia significantly more frequently than the nonexposed group ($p < 0.01$).

The rates of breastfeeding at the different time points are shown in Table 3. There were no statistically significant differences in the proportion of mothers using EBF or PBF at any of the evaluation time points (hospital release, 1, 3, and 6 months). Additionally, there were no differences between EBF and PBF durations between groups.

Discussion

Because of the increasingly frequent administration of synthetic oxytocin during labor and the lack of rigorous studies in this regard, we analyzed data collected in an observational study to evaluate the effects of intrapartum use of this hormone on breastfeeding. Based on previous studies, we expected a relationship between oxytocin administration during labor and the start and duration of breastfeeding. Contrary to our expectations, results did not show statistically significant differences between groups.

Given the variable findings relating synthetic oxytocin administration and breastfeeding found in the literature and in our own studies, many questions arise from these results. The present study results did not replicate those found in a previous study by our group at the same hospital.[20] Several factors may account for the lack of replication. Comparing our two samples reveals differences between the two datasets. For example, in our previous article, all women received epidural anesthesia. In our current data, the oxytocin-exposed group received significantly more epidural analgesia ($p < 0.001$) than the nonexposed group. Several reports observed a negative influence of epidural analgesia on breastfeeding.[21,22] Based on the literature, this difference should have reinforced the negative effect of oxytocin on breastfeeding instead of diminishing the effect. Analgesia is a main confounder in these types of studies given that induction of labor has been associated with greater need for anesthesia.[11]

Another important descriptive data difference is that in our present study, women who received intrapartum oxytocin were more likely to be first-time mothers or to have an assisted delivery. All of those factors have traditionally been associated with shorter breastfeeding duration. However, in our data, we did not find statistically significant differences between groups in the start and duration of breastfeeding. Furthermore, in the first study, we did not have a nonsynthetic oxytocin-exposed group. The current study includes such a control group and adds follow-up measures, as well as it has recruited a larger number of participants (98 compared with 20 in the previous sample).

A possible explanation for our unexpected results could be hospital policies to encourage breastfeeding. It has been shown that in hospitals with policies encouraging breastfeeding, it may be more difficult to assess any adverse effects caused by the use of morphic derivatives during labor.[23] The hospital where the study was carried out is very supportive of breastfeeding, which may explain why oxytocin did not negatively affect breastfeeding rates. The BFHI policies may be a confounding factor and could explain the lack of statistically significant differences. In addition, our data came from a very breastfeeding-motivated sample: one of the inclusion criteria was maternal wish to breastfeed and there was no financial compensation to the study that could add additional motivation to breastfeed.

Another consideration is that the nonoxytocin-exposed group received a higher (not statistically significant) dose of synthetic oxytocin during the third stage of labor, used as recommended to prevent hemorrhage.[24] In a study in the United Kingdom, it was observed that women who received oxytocin during the third stage of labor were more likely to

Table 2. Labor and Delivery Characteristics

Characteristics	*Nonexposed group* (n = *45*)	*Oxytocin-exposed group* (n = *53*)	p
Instrumental delivery	0%	22.4%	0.005
Epidural analgesia	26.2%	95.9%	<0.001
Oxytocin dose during labor (mIU)[a]	0	1,400 (390–4,000)	<0.001
Oxytocin dose after delivery (mIU)[a]	15,000 (10,000–20,000)	10,300 (8,420–17,310)	0.09
Apgar score at 5 minutes[a]	10 (10–10)	10 (10–10)	0.35
Neonatal resuscitation	14.3%	18.4%	0.7

[a]Indicates median (interquartile range).

stop breastfeeding within 48 hours of delivery.[7] The authors controlled for confounding factors, but were limited by the retrospective analysis and lack of long-term follow-up regarding breastfeeding outcomes. Recently, another study showed that mothers who had received uterotonics were significantly less likely to be breastfeeding at 2–6 weeks.[25] How the administration of synthetic oxytocin during the third stage of labor influences breastfeeding remains unknown.

It is surprising that hormonal administration during childbirth is becoming more frequent without empirical and systematic evidence of the possible effects of such administration.[26] There are good reasons to test the effects on breastfeeding given that exogenous oxytocin can potentially affect breastfeeding through various mechanisms, including desensitization and downregulation of myoepithelial receptors and local feedback mechanisms,[27,28] disruption of endogenous pulsatile secretion and fluctuating concentrations,[29] and infant or maternal behavior modification.[20,30]

Our study has several strengths. Based on a review of the literature, there are no other reports about oxytocin dosage in relation to breastfeeding. We also include data from a non-exclusively breastfeeding group and provide follow-up of infant feeding outcomes beyond hospital discharge.

One of the main challenges in studies about perinatal interventions is the possible overlap of confounding factors in the results. For that reason, we only include healthy dyads without perinatal complications to limit risk factors that could have affected the delivery and maternal and neonatal outcomes. Given our restrictive inclusion criteria, the resulting population was a group of uncomplicated healthy neonates. By limiting the analysis to uncomplicated births, we may have precluded the detection of clinically important associations. In addition, this may impact the external validity of the results.

Our study also has several limitations. The main limitation is that the sample was derived from a study designed to assess the effect of synthetic oxytocin intrapartum administration on primitive neonatal reflexes; the size and composition of the sample was thus determined to best evaluate a separate research question. A larger sample size would be needed to lower the likelihood of type 2 errors that could affect our data. Due to our limited sample size and lack of association between synthetic oxytocin intrapartum administration and breastfeeding, we did not analyze the correlations with oxytocin dosage levels. With regard to outcome measures, data pertaining to the first month of life were collected through telephone interviews given at 3 months. This introduces the potential of memory bias, although given the consistency of data from discharge to 6 months, it seems improbable. The large number of missing data (over 20%) at 3 months in the oxytocin-exposed group also reduces the reliability of our results.

Further research is needed to establish the effects of intrapartum hormonal administration on breastfeeding. As Odent

Table 3. Breastfeeding Rates at Different Time Points (Mann–Whitney Nonparametric Test)

Time points	*Nonexposed group*	*Oxytocin-exposed group*	p
Breastfeeding at discharge (%)	*n* = 45	*n* = 53	0.27
EBF	97.2	86.8	
PBF	0	10.5	
FF	2.8	2.6	
Breastfeeding at 1 month (%)			0.80
EBF	81.1	82.1	
PBF	13.5	15.4	
FF	5.4	2.6	
Breastfeeding at 3 months (%)	*n* = 39	*n* = 37	0.78
EBF	70.3	64.1	
PBF	18.9	25.6	
FF	10.8	10.3	
Breastfeeding at 6 months (%)	*n* = 43	*n* = 35	0.52
EBF	31.4	27.9	
PBF	34.3	25.6	
FF	34.3	46.5	
Length of BF (EBF+PBF)[a]	149.2 ± 55.1	148.8 ± 45.3	0.97
Length of EBF[a]	114.7 ± 64.7	119.3 ± 65.1	0.75

[a]Indicates mean ± standard deviation.
EBF, exclusively breastfed; FF, formula feeding; PBF, partially breastfed.

says, there are good reasons to test the hypothesis that earlier than desired cessation of breastfeeding is to a certain extent a phenomenon related to the widespread obstetrical use of synthetic oxytocin.[31] Despite the challenges of longitudinal designs, it would be informative to collect data until babies stop breastfeeding. As mentioned previously, there was a difference between groups in the amount of anesthesia received. It would be useful to conduct this study with patients who did not receive epidural services to remove this confounding factor.

Conclusion

Our data do not support an association between breastfeeding and synthetic oxytocin administered during labor. Given the lack of understanding about the effects of oxytocin administration during delivery and other routines systematically used during labor in maternal breastfeeding, this relationship should be further studied.

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Disclosure Statement

No competing financial interests exist.

References

1. Quigley MA, Kelly YJ, Sacker A. Breastfeeding and hospitalization for diarrheal and respiratory infection in the United Kingdom Millennium Cohort Study. *Pediatrics* 2007;119:e837–e842.
2. Lucas A, Morley R, Cole TJ, et al. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 1992;339:261–264.
3. Edmond KM, Zandoh C, Quigley MA, et al. Delayed breastfeeding initiation increases risk of neonatal mortality. *Pediatrics* 2006;117:e380–e386.
4. Jaafar SH, Lee KS, Ho JJ. Separate care for new mother and infant versus rooming-in for increasing the duration of breastfeeding. *Cochrane Database Syst Rev* 2012;9:CD006641.
5. Smith LJ. Impact of birthing practices on the breastfeeding dyad. *J Midwifery Womens Health* 2007;52:621–630.
6. Devroe S, De Coster J, Van de Velde M. Breastfeeding and epidural analgesia during labour. *Curr Opin Anaesthesiol* 2009;22:327–329.
7. Jordan S, Emery S, Watkins A, et al. Associations of drugs routinely given in labour with breastfeeding at 48 hours: Analysis of the Cardiff births survey. *BJOG* 2009;116:1622–1629.
8. Freeman RK, Nageotte M. A protocol for use of oxytocin. *Am J Obstet Gynecol* 2007;197:445–446.
9. Clark SL, Simpson KR, Knox GE, et al. Oxytocin: New perspectives on an old drug. *Am J Obstet Gynecol* 2009; 200:35.e1–e6.
10. Medication during pregnancy: An intercontinental cooperative study. Collaborative Group on Drug Use in Pregnancy (C.G.D.U.P.). *Int J Gynaecol Obstet* 1992;39:185–196.
11. Guerra GV, Cecatti JG, Souza JP, et al. Elective induction versus spontaneous labour in Latin America. *Bull World Health Organ* 2011;89:657–665.
12. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. *J Matern Fetal Med* 1996;5:245–255.
13. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders?—A look at the literature. *Med Hypotheses* 2004;63:456–460.
14. Ounsted MK, Hendrick AM, Mutch LM, et al. Induction of labour by different methods in primiparous women. I Some perinatal and postnatal problems. *Early Hum Dev* 1978;2: 227–239.
15. Out JJ, Vierhout ME, Wallenburg HCS. Breast-feeding following spontaneous and induced labour. *Eur J Obstet Gynecol Reprod Biol* 1988;29:275–279.
16. Garcia-Fortea P, Gonzalez-Mesa E, Blasco M, et al. Oxytocin administered during labor and breast-feeding: A retrospective cohort study. *J Matern Fetal Neonatal Med* 2014;27:1598–1603.
17. Bai DL, Wu KM, Tarrant M. Association between intrapartum interventions and breastfeeding duration. *J Midwifery Womens Health* 2013;58:25–32.
18. Marín Gabriel MA, Olza Fernández I, Malalana Martínez AM, et al. Intrapartum synthetic oxytocin reduce the expression of primitive reflexes associated with breastfeeding. *Breastfeed Med* 2015;10:209–213.
19. IBM-Corporation. IBM SPSS Statistics for Windows, Version 14.0. Armonk, NY: IBM Corporation, 2005.
20. Olza Fernandez I, Marin Gabriel M, Malalana Martinez A, et al. Newborn feeding behaviour depressed by intrapartum oxytocin: A pilot study. *Acta Paediatr* 2012;101:749–754.
21. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. *Cochrane Database Syst Rev* 2011:CD000331.
22. Volmanen P, Valanne J, Alahuhta S. Breast-feeding problems after epidural analgesia for labour: A retrospective cohort study of pain, obstetrical procedures and breastfeeding practices. *Int J Obstet Anesth* 2004;13:25–29.
23. Halpern SH, Levine T, Wilson DB, et al. Effect of labor analgesia on breastfeeding success. *Birth* 1999;26:83–88.
24. Begley CM, Gyte GM, Murphy DJ, et al. Active versus expectant management for women in the third stage of labour. *Cochrane Database Syst Rev* 2010:CD007412.
25. Brown A, Jordan S. Active management of the third stage of labor may reduce breastfeeding duration due to pain and physical complications. *Breastfeed Med* 2014;9:494–502.
26. Nabi HA, Aflaifel NB, Weeks AD. A hundred years of induction of labour methods. *Eur J Obstet Gynecol Reprod Biol* 2014;179:236–239.
27. Cassoni P, Marrocco T, Sapino A, et al. Oxytocin synthesis within the normal and neoplastic breast: First evidence of a local peptide source. *Int J Oncol* 2006;28:1263–1268.
28. Leng G, Caquineau C, Sabatier N. Regulation of oxytocin secretion. *Vitam Horm* 2005;71:27–58.
29. Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. *Curr Opin Pharmacol* 2008;8:731–734.
30. Carter CS. Developmental consequences of oxytocin. *Physiol Behav* 2003;79:383–397.
31. Odent MR. Synthetic oxytocin and breastfeeding: Reasons for testing an hypothesis. *Med Hypotheses* 2013;81:889–891.

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ANEXO 7. Artículo revista Women and Birth (aceptado para publicación). “Cessation of breastfeeding in association with oxytocin administration and type of birth. A prospective cohort study”.

Title: Cessation of Breastfeeding in Association with Oxytocin Administration and Type of Birth. A prospective cohort study.

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Conflict of Interest: none

Cessation of Breastfeeding in Association with Oxytocin Administration and Type of Birth. A prospective cohort study

Abstract

Background: Some studies have suggested an association between synthetic oxytocin administration and type of birth with the initiation and consolidation of breastfeeding.

Aim: This study aimed to test whether oxytocin administration and type of birth are associated with cessation of exclusive breastfeeding at different periods. A second objective was to investigate whether the administered oxytocin dose is associated with cessation of exclusive breastfeeding.

Methods: We conducted a prospective cohort study (n=529) in a tertiary hospital. Only full-term singleton pregnancies were included. Four groups were established based on the type of birth (vaginal or cesarean) and the intrapartum administration of oxytocin. Follow-up was performed to evaluate the consolidation of exclusive breastfeeding at 1, 3 and 6 months.

Findings: During follow-up, the proportion of exclusive breastfeeding decreased in all groups. After adjusting for confounding variables, the group with cesarean birth without oxytocin (planned cesarean birth) had the highest risk of cessation of exclusive breastfeeding (odds ratio [95% confidence interval], 2.51 [1.53-4.12]). No association was found between the oxytocin dose administered during birth and puerperium period and the cessation of exclusive breastfeeding.

Conclusion: Planned cesarean birth without oxytocin is associated with the cessation of exclusive breastfeeding at 1, 3 and 6 months of life. It would be desirable to limit elective caesarean births to essentials as well as to give maximum support to encourage

breastfeeding in this group of women. The dose of oxytocin given during birth and puerperium period is not associated with cessation of exclusive breastfeeding.

Keywords: breast feeding; parturition; oxytocin; postpartum period.

Statement of Significance

Problem or Issue	Synthetic oxytocin and type of birth may affect breastfeeding, but there are few prospective studies about this topic.
What is Already Known	Oxytocin and type of birth have been related to the cessation of breastfeeding. Planned cesarean birth is related to a cessation of exclusive breastfeeding.
What this Paper Adds	Oxytocin is not related to a cessation of exclusive breastfeeding. Planned cesarean birth without oxytocin is associated with the cessation of exclusive breastfeeding.

Background

Oxytocin is a nine amino-acid peptide (nonapeptide) hormone that is produced in the hypothalamus. During pregnancy, oxytocin receptors are expressed in the myometrium and in the mammary glands. Oxytocin receptors can also be found in several regions of the central nervous system, such as the preoptic area of the hypothalamus, the amygdala and the insula.[1] In addition to its known effects on uterine contraction and milk ejection during nursing, oxytocin also plays a central role in the control of social behavior, including sexual behavior, child bonding, social memory and recognition.[2,3]

The initiation of lactation, milk ejection and child bonding depend, among other things, on the secretion of oxytocin from the posterior hypophysis,[4,5] in addition to that generated by the myoepithelial cells through a local mechanism of positive feedback.[6] Oxytocin is released in a pulsatile manner that increases in frequency during physiological labor, reaching a maximum level in the maternal brain in the hour after childbirth.[7] The induction of labor with oxytocin and planned cesarean birth may alter the physiological neurohormonal stage of the mother and also the oxytocin balance in the newborn. Studies in other mammals have shown that the manipulation of perinatal peptides in offspring has long-term effects on social and sexual behavior.[8] There is a tendency to accept that the effects of exogenous synthetic oxytocin are well established and benign; however, it is the drug most frequently associated with preventable or avoidable adverse perinatal outcome during labor.[9]

The impact of synthetic oxytocin on breastfeeding has not been studied in depth.[10] Exogenous oxytocin administration may alter the onset of breastfeeding in several ways: by altering the pulse frequency of endogenous oxytocin and its secretion,[11,7] by desensitizing oxytocin receptors[12] and, more speculatively, by altering infantile or maternal behavior.[13,14] Moreover, intrapartum administration of synthetic oxytocin has

been shown to decrease endogenous oxytocin levels during the second day postpartum and to increase the levels of prolactin.[15] In our previous studies, albeit with a small sample size, we observed an inverse relationship between exogenous oxytocin administration and the percentage of exclusive breastfeeding at 3 months of age.[16,17]

In a similar vein, cesarean birth involves the manipulation of the neurobiology of labor. In the context of elective cesarean birth, the effect that the pulsatile release of oxytocin has on uterine dynamics during spontaneous labor does not occur. Furthermore, the descent of the fetal head through the birth canal does not take place, which is a stimulus for the release of maternal oxytocin. In addition, because the fetal head is not compressed in the birth canal, the newborn does not release stress-inducing substances (catecholamines and cortisol) that are responsible for changing the level of alertness in the first few hours after birth. In experimental studies with mammals, it has been observed that mothers may be indifferent towards newborns after a planned cesarean, an outcome that has been related to the absence of oxytocin.[10] Several studies assert that elective cesarean birth can have a negative impact on breastfeeding rates, and while on many occasions this is related to the aforementioned neurohormonal mechanisms, other factors such as mother-child separation or the non-accomplishment of skin-to-skin contact during the surgical procedure may also influence this outcome.[18]

According to the World Health Organization (WHO), mother´s milk contains all the nutrients and energy a child needs in the first months of life, and continues to supply one half or more of the child´s nutritional needs during the second half year, and up to one third during the second year. Moreover, it promotes sensory and cognitive development and protects the child from infectious and chronic diseases.[19,20]

Given the above, it is important to identify those factors of labor that can modify the duration/consolidation of breastfeeding. The principal objective of the present study was

thus to assess the possible association of intrapartum oxytocin administration and the mode of birth with cessation of exclusive breastfeeding at 1, 3 and 6 months of life. The secondary objective was to assess whether administration of oxytocin during the puerperium was associated with cessation of exclusive breastfeeding during these periods.

Participants, Ethics and Methods

A prospective cohort study (n=529) was carried out in a tertiary hospital in Madrid, Spain, with the Baby-Friendly Hospital Initiative (BFHI) award, and with >3,000 births per year. Four groups were established based on the mode of birth and intrapartum oxytocin administration: the first group comprised dyads who underwent vaginal birth without the use of oxytocin (vb-ox); the second group were dyads with vaginal birth with the use of oxytocin (vb+ox); the third group were dyads with cesarean birth with oxytocin (cb+ox); and the fourth group were dyads with planned cesarean birth without oxytocin (cb-ox). Inclusion criteria were single full-term gestation, newborn with Apgar score >7 at 5 minutes, prenatal wish to breastfeed, and informed signed consent before birth. Exclusion criteria were the following: preterm newborn, fetal chromosomopathies or other anomalies that could impact adaptation to the extra uterine environment, admission of the mother/newborn to the intensive care unit in the first 48 hours of life, prenatal intention or desire to administer formula, general anesthesia, and having an insufficient understanding of Spanish. The Local Ethics Committee approved the study.

The following demographic variables and variables related to the labor process and to infant follow-up were collected: maternal age, nationality, marital status, educational attainment, prenatal education, parity, gestational age, use of locoregional analgesia

during childbirth, gender and weight of the newborn, pacifier use, attendance to a breastfeeding support group, and re-integration into the workplace.

The procedure during the labor was the following: for births with a spontaneous onset, exogenous oxytocin was not administered unless the uterine dynamic was poor. When there was a medical indication to end gestation, labor was induced with intravenous oxytocin. To administer oxytocin, a vial of 10 UI (Syntocinon®, Sigma Tau) was diluted into 500 ml of saline solution. This was given to the woman at a rate of 1 mUI/minute and the dose was doubled every 20 minutes until achieving at least 3 contractions every 10 minutes. The maximum recommended dose was 32 mUI/minute (Cardiff Method[21]).

Active management measures were introduced in the third phase of labor. After the birth of the anterior fetal shoulder, 5 UI of oxytocin was administered through a venous catheter. Oxytocin administration was maintained at a rate of 2 UI/hour for the first two hours postpartum. In the case of cesarean birth, 3 UI of oxytocin was administered through a venous catheter after birth, and an additional 10 UI of oxytocin was administered during the first hour postpartum. When the woman requested locoregional analgesia to control labor pain, an epidural catheter was placed after receiving informed consent. Anesthesia was induced with 0.125% levobupivacaine (Normon) plus fentanyl or 0.2% ropivacaine (Inibsa) plus fentanyl.

For vaginal births, when the newborns did not need cardiopulmonary resuscitation, they were dried, identified and placed skin-to-skin with their mothers during 90 minutes. After this time, routine measurements were performed (weight, size, cephalic perimeter, eye prophylaxis and anti-hemorrhagic prophylaxis). If the newborn had not latched on the breast spontaneously, both mother and child were aligned to begin breastfeeding. In the case of cesarean births, when maternal and/or fetal conditions permitted, skin-to-

skin contact took place during the surgical procedure and also at the Postoperative Care Unit. On the occasions when this was not possible, such contact took place after surgery at the Postoperative Care Unit (in the first 60 minutes of life). Under no circumstances was the newborn infant placed in a different room from the mother. During the hospital stay, the nursing staff offered advice on breastfeeding, encouraging the proper positioning of the newborn to latch onto the mother's breast and answering questions about the process. Likewise, after discharge from hospital, mothers could call a nursing advice line 24 hours a day, 7 days a week, for breastfeeding consultation.

To collect data on the dose of oxytocin administered during labor and birth, an investigator of the team completed a questionnaire. Telephone calls were made at 3 and 6 months of life to record the duration of breastfeeding.

The study considered exclusive breastfeeding at 1 and 3 months of life when the infants had been fed only by breastfeeding, and at 6 months when they had been breastfed with or without the introduction of complementary feeding. Loss of follow-up was regarded as 5 unsuccessful telephone attempts. After 3 months, 6 dyads (1.1%) were considered lost, and 17 (3.2%) after 6 months.

Sample size estimation: to achieve differences by means of a Chi-squared test, over cessation of exclusive breastfeeding between the oxytocin administrated cohort (46%) and non-exposed to oxytocin cohort (34%) (based on a previous pilot study), given a 95% confidence level and 80% power, a balance between the two cohorts of 55%, we needed to recruit 294 women with administration of oxytocin and 235 women with no oxytocin administration. Descriptive analyses were performed using absolute and relative frequencies for categorical variables, and mean (standard deviation) or median (25^{th}-75^{th} percentiles) for numerical variables. Comparisons of baseline characteristics and between the four groups were performed using the Kruskal-Wallis test or the chi-

squared test. To assess the association between the exposure group and cessation of exclusive breastfeeding along the follow-up, a generalized estimating equation (GEE) analysis was performed.[22] This analysis considers the different measures along the time for each woman and takes into account the consequent correlation. The dependent variable was cessation of exclusive breastfeeding at each time point of follow-up: at discharge, 1 month, 3 months and 6 months. A logit link function was applied and the covariance structure was autoregressive order 1. We first examined crude associations which, when found, were adjusted for possible confounding variables that, by clinical or statistical criteria, helped to assess whether the association was due to confounding variables. The Pearson correlation coefficient was used to test the correlation between oxytocin dose and duration of exclusive breastfeeding. The significance level was established at 0.05. Statistical analysis was carried out using Stata/IC v.14.1. (StataCorp LP, College Station, TX).

Findings

The characteristics of each of the four study groups are shown in Table 1. We observed that the vb-ox group received locoregional analgesia with less frequency. We also observed differences between groups for gestational age, parity and prenatal education.

At hospital discharge, the proportion of mothers exclusively breastfeeding was 90.7% in the vb-ox group, 85.5% in the vb+ox group, 87% in the cb+ox group and 82.5% in the cb-ox group. The proportion of mothers who exclusively breastfed at 1, 3 and 6 months decreased across all groups: 84.1%, 70.2% and 39.9%, respectively, in the vb-ox group; 79.9%, 66.2% and 29.2% in the vb+ox group; 78.2%, 60.9% and 22.7% in the cb+ox group; and 70%, 48.7% and 25.6% in the cb-ox group. Differences between groups were statistically significant at 3 and 6 months (Figure 1).

For further analysis, we conducted a GEE regression analysis to test for associations between the administration of synthetic oxytocin, mode of birth and cessation of exclusive breastfeeding during the follow-up. Using the vb-ox group as a reference, no differences were observed for cessation of exclusive breastfeeding throughout the follow-up in the vb+ox and cb+ox groups; however, we observed an increased risk to cease exclusive breastfeeding in the cb-ox group, (odds ratio [OR] 2.21; 95% confidence interval [CI] 1.37-3.56) (Table 2).

When the same analysis was carried out considering confounding factors that we have recently associated with the cessation from exclusive breastfeeding (absence of a college degree, pacifier use, re-integration into the workplace, primiparity, and not having attended a breastfeeding support group[23]), we found that the cb-ox group was more at risk of abandoning exclusive breastfeeding during the follow-up than the other groups (OR 2.51; 95% CI 1.53-4.12) (Table 2).

No association was found between the dose of oxytocin given at birth (mean=2863.7; SD=3782 mUI) and cessation of exclusive breastfeeding at 3 (OR 1.01; 95% CI 0.94-1.07; p=0.73) and 6 (OR 1.01; 95% CI 0.95-1.08; p=0.55) months. Similarly, no association was found between the dose of oxytocin given during the puerperium (mean=12475.52; SD=6128.3 mU) and cessation of exclusive breastfeeding at 3 (OR 0.97; 95% CI 0.94-1.00; p=0.06) and 6 (OR 0.99; 95% CI 0.96-1.02; p=0.9) months.

Discussion

The results of the present study show that administration of synthetic oxytocin during labor is not associated with cessation of exclusive breastfeeding at the time points analyzed.

The study of the use of exogenous oxytocin during labor and its consequences for breastfeeding is our main field of research. It is commonly considered that there are two barriers that potentially impede the flow of oxytocin to the fetal brain: the materno-placental barrier and the blood-brain barrier. The placental barrier contains oxytocinase (cysteine aminopeptidase), which can effectively degrade oxytocin. Studies on the materno-fetal and feto-maternal diffusion of oxytocin have shown that oxytocin transport is greater in the materno-fetal direction; accordingly, oxytocin administered to the mother could reach fetal circulation.[24] Regarding the blood-brain barrier, early studies indicated that oxytocin does not cross the blood-brain barrier, but the stress experienced by mother and baby during childbirth could provoke an increase in cytokine release (oxidative stress), making the blood-brain barrier more permeable than usual.[25] Therefore, synthetic oxytocin administered to the mother could reach the fetal brain.[26]

We have previously shown that mothers that discontinued exclusive breastfeeding after 1 and 3 months after birth had received higher doses of oxytocin during labor than those that maintained breastfeeding.[16] However, in a later study, we failed to find statistically significant differences between intralabor synthetic oxytocin administration and the onset and duration of exclusive breastfeeding.[27]

Here, we analyzed both the dose of oxytocin administered before fetal birth (dilation and expulsion) and the dose administered within the first 2 hours after labor (childbirth and early puerperium), and we found no association between the dose of oxytocin administered during labor and cessation of exclusive breastfeeding at 1, 3 and 6 months of life. However, the vb-ox group showed a higher proportion for exclusive breastfeeding at 3 and 6 months (70.2% and 39.9%, respectively) as compared with the

groups that had received oxytocin (66.2% and 29.2%, respectively, in the vb+ox group, and 60.9% and 22.7%, respectively, in the cb+ox group).

A retrospective study carried out in Spain in 2014 with 316 women[28], found that oxytocin administered during labour was associated with an increased risk for cessation of breastfeeding at 3 months by 2.29 (this factor was dependent on maternal age, and was higher for women under 27 years old). A possible explanation for the difference between this report and our present study is that the previously mentioned study was carried out in a tertiary hospital without BFHI acreditation. In line with our findings, a recent study performed in Canada (n=386) found that mothers who maintained exclusive breastfeeding after 2 months were those who had received lower doses of synthetic oxytocin during labor.[29]

Regarding oxytocin administration within the first 2 hours after labor (birth and early puerperium), no association was found between the dose administered and cessation of exclusive breastfeeding at 3 and 6 months of life. Previous studies point to a relationship between oxytocin administration during the puerperium and cessation of breastfeeding. Brown et al[30] performed a retrospective study with 288 women and observed that prophylactic oxytocin administration during birth was related to a lower percentage of breastfeeding at 2 and 6 weeks post-labor. Likewise, in retrospective cohort study Jordan et al found a lower percentage of breastfeeding when oxytocin had been administered to avoid post-labor hemorrhage.[31]

Regarding the mode of birth and its possible association with cessation of exclusive breastfeeding, our results show a relationship between planned caesarian birth and cessation of breastfeeding, both at 3 and 6 months of life, although the percentage of exclusive breastfeeding in this group was already lower at hospital discharge. Thus, at 3 months, the percentage of exclusive breastfeeding was 70.2% in the vb-ox group and

48.7% in the cb-ox group; at 6 months, this dropped to 39.9% in the vb-ox group and 25.6% in the cb-ox group.

In a recent prospective study by Hobbs et al[32] performed in a region of Canada, which included 3021 women, the authors analyzed the relationship between the mode of birth and the onset and duration of breastfeeding. The results showed an association between elective cesarean and cessation of breastfeeding within the first 4 months of life. In addition, a multicenter research study carried out in the north of Italy[33] analyzed 9306 mothers in a retrospective manner, and found a relationship between elective cesarean and breastfeeding failure.

There are some limitations to the present study. There was a selection bias since all the women expressed a desire to breastfeed before the labor, and only singleton term gestations were included. Despite this, we considered it important to investigate an association between oxytocin administration and mode of birth and the early cessation of exclusive breastfeeding when mothers had previously shown a desire to breastfeed, as they were presumably more motivated to initiate and maintain breastfeeding. Also, the study was performed in a hospital with a BFHI acreditation. These constraints may minimize the impact of the factors analyzed regarding cessation of exclusive breastfeeding and reduce the external validity. In addition, the percentage of women that recieved local analgesia changed between groups. In this regard, a study by French et al pointed to a relationship between this method of pain relief and worse breastfeeding outcomes.[34] Moreover, the average gestational age at labor was also different between groups, although we did not consider these data clinically relevant. There was also a memory bias that could limit the validity of the study, since the information regarding the type of feeding was collected retrospectively at 3 and 6 months after birth. However, there is evidence to support the reliability in these questionaires.[35] The lack of follow-up

may limit the impact of the findings, but because this was minimum (1.1% and 3.2% at 3 and 6 months, respectively), we consider that it did not modify the results observed. Another limitation is that we considered exclusive breastfeeding at 6 months with mother´s milk, with or without the introduction of complementary foods. Finally, maintenance of exclusive breastfeeding at 6 months of life could be affected by the legal rights in Spain, since paid maternity leave lasts only for 16 weeks.

Conclusion

In our study, birth by cesarean section without administered oxytocin is associated with cessation of exclusive breastfeeding at 1, 3 and 6 months of life. It would be desirable to limit elective caesarean sections to essentials as well as to give maximum support to encourage breastfeeding in this group of women.

Oxytocin administration during labor is not associated with cessation of exclusive breastfeeding at the different time points studied. However, lower percentages of exclusive breastfeeding were observed when the mothers received synthetic oxytocin.

The dose of oxytocin administered during the first 2 hours after childbirth (birth and early puerperium) was not associated with cessation of exclusive breastfeeding, although the percentage of mothers that continued exclusive breastfeeding at 3 months tended to decrease as the doses of administered oxytocin increased. Taking these results together, we consider that more research is needed to better understand the effects of the use of synthetic oxytocin on breastfeeding.

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References

1. Bosch OJ, Neumann ID. Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. Horm Behav. 2012;61(3):293-303.
2. Carter CS, Williams JR, Witt DM, Insel TR. Oxytocin and social bonding. *Ann N Y Acad Sci*. 1992;652:204-11.
3. Insel TR, Young LJ. The neurobiology of attachment. *Nat Rev Neurosci*. 2001; 2(2):129-36.
4. Nissen E, Lilja G, Widstrom AM, Uvnas-Moberg K. Elevation of oxytocin levels early post partum in women. Acta Obstet Gynecol Scand. 1995;74(7):530-3.
5. Winberg J. Mother and newborn baby: mutual regulation of physiology and behavior, a selective review. Dev Psychobiol. 2005;47(3):217-29.
6. Cassoni P, Marrocco T, Sapino A, Allia E, Bussolati G. Oxytocin synthesis within the normal and neoplastic breast: first evidence of a local peptide source. Int J Onco. 2006;28(5):1263-8.
7. Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity, adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. Prog Brain Res. 2001;133:1-38.
8. Henry S, Richard-Yris MA, Tordjman S, Hausberger M. Neonatal handling affects durably bonding and social development. PLoS One. 2009;4(4):e5216.
9. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009;200(1):35.e1-35.e6.
10. Carter CS. Developmental consequences of oxytocin. Physiol Behav. 2003; 79(3):383-97.

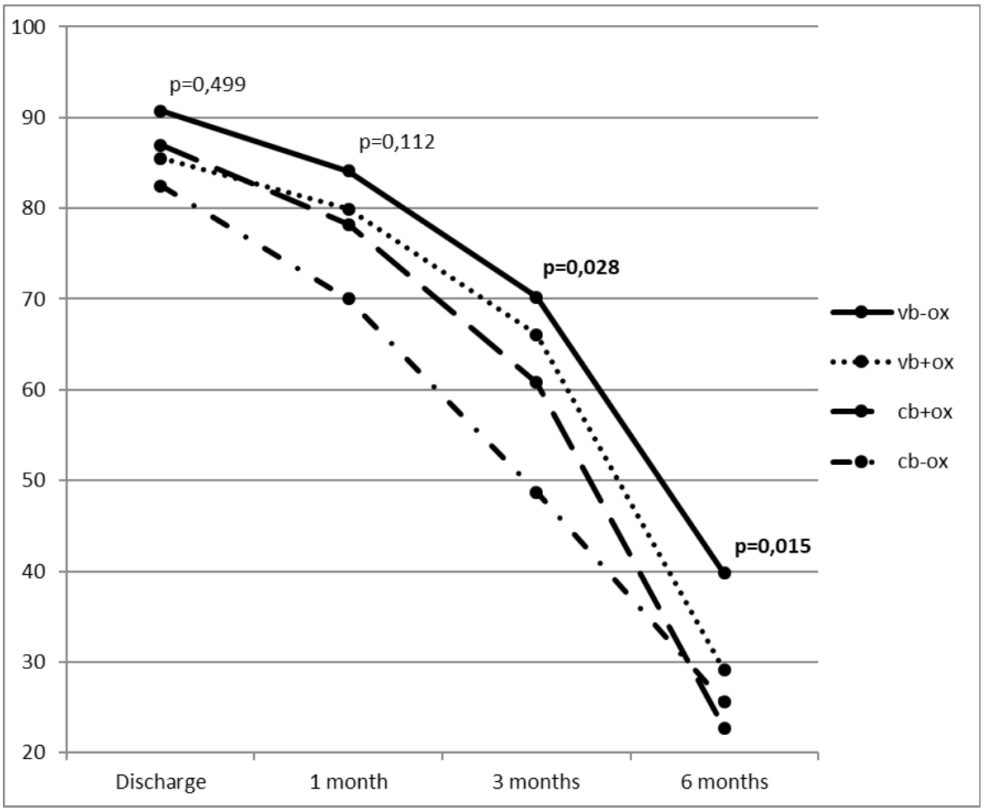
11. Nissen E, Uvnas-Moberg K, Svensson K, Stock S, Widstrom AM, Winberg J. Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route. Early Hum Dev. 1996;5;45(1-2):103-18.
12. Reversi A, Cassoni P, Chini B. Oxytocin receptor signaling in myoepithelial and cancer cells. J Mammary Gland Biol Neoplasia. 2005;10(3):221-9.
13. Jonas W, Nissen E, Ransjo-Arvidson AB, Matthiesen AS, Uvnas-Moberg K. Influence of oxytocin or epidural analgesia on personality profile in breastfeeding women: a comparative study. Arch Womens Ment Health. 2008;11(5-6):335-45.
14. Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. Curr Opin Pharmacol. 2008;8(6):731-4.
15. Jonas K, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidson AB, Uvnäs-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. *Breastfeed Med*. 2009;4(2):71-82.
16. Marín MA, Olza I, Malalana A, Martínez B, Fernández-Cañadas A. Influencia de la oxitocina administrada durante el parto en el mantenimiento de la lactancia materna. Estudio Preliminar. Acta Pediatr Esp. 2012;70(11):269-71.
17. Olza I, Marín MA, Malalana A, Fernández-Cañadas A, López F, Costarelli V. Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. Acta Paediatr. 2012;101(7):749-54
18. Olza-Fernández I, Marín Gabriel MA, Gil-Sanchez A, Garcia-Segura LM, Arevalo MA. Neuroendocrinology of childbirth and mother-child attachment:

the basis of an etiopathogenic model of perinatal neurobiological disorders. Front Neuroendocrino. 2014;35(4):459-72.

19. Organización Mundial de la Salud. Lactancia materna exclusiva. 2017. Available at http://www.who.int/nutrition/topics/exclusive_breastfeeding/es/ [accessed January 26, 2018].
20. Organización Mundial de la Salud. Alimentación del lactante y del niño pequeño. 2016. Available at http://www.who.int/mediacentre/factsheets/fs342/es/ [accessed January 26, 2018].
21. Usandizaga JA, De la Fuente P. Obstetricia y Ginecología. Madrid: Marbán, 2011. ISBN: 978-84-7101-738-3.
22. Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: an orientation. Am J Epidemiol. 2003;157(4):364-75.
23. Fernández-Cañadas A, Durán M, Hernández AB, Muriel C, Martínez B, Oscoz A, et al. A comparison of factors associated with cessation of exclusive breastfeeding at 3 and 6 months. Breastfeed Med. 2017;12(7):430-5.
24. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. J Matern Fetal Med. 1996;5(5):245-55.
25. Banks WA, Kastin AJ. Bidirectional passage of peptides across the blood-brain barrier. Prog Brain Res. 1992;91:139-48.
26. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders? A look at the literature. Med Hypotheses. 2004; 63(3):456-60.

27. Fernández-Cañadas A, Marín MA, Olza I, Martínez B, Durán M, Malalana A, et al. The relationship of the administration of intrapartum synthetic oxytocin and breastfeeding initiation and duration rates. Breastfeed Med. 2017;12:98-102.
28. Garcia-Fortea P, Gonzalez-Mesa E, Blasco M, Cazorla O, Delgado-Rios M, Gonzalez-Valenzuela MJ. Oxytocin administered during labor and breast-feeding: a retrospective cohort study. J Matern Fetal Neonatal Med. 2014;27(15):1598-603.
29. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, et al. Intrapartum synthetic oxytocin and its effects on maternal well-being al 2 months postpartum. Birth. 2016;43:28-35.
30. Brown A, Jordan S. Active management of the third stage of labor may reduce breastfeeding duration due to pain and physical complications. Breastfeed Med. 2014;9:494-502.
31. Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Association of drugs routinely given in labour with breastfeeding at 48 hours: analysis of de Cardiff Births Survey. BJOG. 2009;116:1622-9.
32. Hobbs AJ, Mannion CA, McDonald SW, Brockway M, Tough SC. The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. BMC Pregnancy and Chidbirth. 2016;16:90.
33. Zanardo V, Pigozzo A, Wainer G, Marchesoni D, Gasparoni A, Di Fabio S, et al. Early lactation failure and formula adoption after elective caesarean delivery: cohort study. Arch Dis Child Fetal Neonatal Ed. 2013;98:F37-41.
34. French CA, Cong X, Chung KS. Labor epidural analgesia and breastfeeding: a systematic review. J Hum Lact. 2016;32:507-20.

35. Natland ST, Andersen LF, Nilsen TI, Forsmo S, Jacobsen GW. Maternal recall of breastfeeding duration twenty years after delivery. BMC Med Res Methodol. 2012;12:179.



vb-ox: vaginal birth without oxytocin

vb+ox: vaginal birth with oxytocin

cb+ox: cesarean birth with oxytocin

cb-ox: cesarean birth without oxytocin

Table 1. Sample characteristics expressed as absolute (percentages), mean (standard deviation), or median (interquartile range).

Sample characteristics (n=529)					
	vb-ox (n=153)	**vb+ox** (n=270)	**cb+ox** (n=24)	**cb-ox** (n=82)	***p***
Childbirth factors					
Locoregional analgesia	122 (79.7%)	263 (97.4%)	24 (100%)	82 (100%)	<0.001
Gestational age (weeks), M (SD)	39.2 (0.9)	39.4 (1.2)	39.8 (1)	38.7 (0.9)	<0.001
Newborn weight (grams), M (SD)	3,238.5 (396.3)	3,290.9 (393.6)	3,271.4 (385.8)	3,300.8 (433.7)	0.687
Sociodemographic factors					
Age (years), M (SD)	33.4 (4.4)	33.9 (4.2)	35.1 (4)	34.5 (4.7)	0.070
Spanish nationality	129 (84.3%)	246 (91.1%)	21 (87.5%)	69 (84.1%)	0.135
University studies	103 (67.3%)	186 (68.9%)	14 (58.3%)	53 (64.6%)	0.694
Primiparity	40 (26.1%)	138 (51.1%)	15 (62.5%)	34 (41.5%)	<0.001
Prenatal education	78 (51%)	172 (63.7%)	17 (70.8%)	40 (48.8%)	0.011
Couple	152 (99.3%)	269 (99.6%)	24 (100%)	79 (96.3%)	0.051
Newborn sex: female	76 (49.7%)	152 (56.3%)	10 (41.7%)	45 (54.9%)	0.367
Apgar test 5 minutes, median (IQR)	10 (10-10)	10 (10-10)	10 (10-10)	10 (10-10)	0.384

Abbreviations: vb, vaginal birth; ox, oxytocin; cb, cesarean birth

Table 2. Association between mode of birth/administration of oxytocin and cessation of exclusive breastfeeding among the times analyzed (1, 3 and 6 months of life).

	UNADJUSTED ANALYSIS		**ADJUSTED ANALYSIS***	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
vb-ox	Reference category	-	Reference category	-
vb+ox	1.43 (1.00-2.05)	0.049	1.35 (0.92-1.96)	0.119
cb+ox	1.74 (0.80-3.76)	0.157	1.25 (0.56-2.80)	0.576
cb-ox	2.21 (1.37-3.56)	0.001	2.51 (1.53-4.12)	<0.001

*Analysis adjusted according to confounding variables (lack of university studies, pacifier use, re-incorporation into the workplace, primiparity and non-attendance to a breastfeeding support group).

Abbreviations: vb, vaginal birth; ox, oxytocin; cb, cesarean birth

ANEXO 8. Artículo revista Breastfeeding Medicine. “A comparison of factors associated with cessation of exclusive breastfeeding at 3 and 6 months”.

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Clinical Research

A Comparison of Factors Associated with Cessation of Exclusive Breastfeeding at 3 and 6 Months

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Abstract

Aim: To analyze the association of labor and sociodemographic factors with cessation of exclusive breastfeeding (EBF) at 3 and 6 months of life.
Materials and Methods: A prospective cohort study ($n = 529$) was performed in a tertiary hospital with the Baby-Friendly Hospital Initiative (BFHI) award. Labor and sociodemographic factors were investigated. Single-term newborns were included. After 3 and 6 months, telephone calls were made to determine the type of lactation. Univariate analysis was performed with the chi-square test or Fisher's exact test. Multivariable logistic regression models were developed to determine risk factors associated with cessation of breastfeeding at 3 and 6 months.
Results: At 3 months, 523 participants (98.9%) were contacted, of whom 64.4% maintained EBF. Factors associated with cessation were pacifier use (odds ratio [OR] 3.49; 95% confidence interval [95% CI] 2.24–5.43), cesarean delivery (OR 4.49; 95% CI 2.96–6.83), no college degree (OR 2.01; 95% CI 1.35–3.01), and not attending breastfeeding support groups (OR 1.96; 95% CI 1.22–3.12). At 6 months, 512 participants (96.8%) were contacted, of whom 31.4% maintained EBF. Factors associated with cessation were reintegration into the workplace (OR 4.49; 95% CI 2.96–6.83), pacifier use (OR 3.49; 95% CI 2.24–5.43), and primiparity (OR 1.61; 95% CI 1.05–2.46).
Conclusions: Several risk factors are associated with the premature cessation of EBF. There is a need to define strategies to correct modifiable factors and to promote protective factors with the aim of improving the success rate of EBF to reach the recommendations of the World Health Organization.

Keywords: breastfeeding, cessation, labor factors, sociodemographic factors

Introduction

EXCLUSIVE BREASTFEEDING (EBF) during the first 6 months of life provides many benefits to both mother and child. Breast milk promotes sensory and cognitive development and protects the infant against infectious and chronic diseases. It is also an important source of energy and nutrients to infants between 6 and 23 months.[1]

The World Health Organization (WHO) recommends EBF during the first 6 months of life, the introduction of food that is safe and appropriate after that age, and to maintain breastfeeding until 2 years or more.[2]

No official monitoring system for breastfeeding exists in Spain; however, several reports published in the last decade indicate that the frequency and duration of breastfeeding do not reach the levels recommended by the WHO.[3,4]

According to the last Spanish Health Survey conducted by the National Statistical Institute between 2011 and 2012, the percentage of breastfeeding is 51% at 3 months of life and 26% at 6 months of life.[5] A study carried out by Rius et al. in

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2005, in a region in eastern Spain, showed that the maintenance of breastfeeding at 3 and 6 months of age was 39% and 21%, respectively.[4] In other European countries, EBF rates at 6 months are 34% (Portugal), 17.2% (Denmark), 14% (Sweden), and 5% (Italy).[6]

To improve EBF rates in Spain, we sought to identify factors that might lead to cessation of breastfeeding and the introduction of formula feeding. Previous studies have shown that some factors related to labor may affect breastfeeding, including administration of synthetic oxytocin, mode of delivery, and epidural analgesia.[7,8] Other studies have found correlations between the abandonment of breastfeeding and several sociodemographic factors, such as maternal age, no college degree, primiparity, gestational age, absence of prenatal education, gender of the newborn, pacifier use, not having attended a breastfeeding support group, and reintegration into the workplace.[9,10]

The aim of the current study is to evaluate the association of labor and sociodemographic factors with the cessation of EBF at 3 and 6 months of life.

Materials and Methods

A prospective cohort study ($n = 529$) was carried out in a tertiary hospital in Madrid, Spain, with the Baby-Friendly Hospital Initiative (BFHI) award and with more than 3,000 deliveries per year.

Inclusion criteria were single full-term gestation, Apgar score >7 at 5 minutes, and prenatal intention or wish to breastfeed.

Exclusion criteria were the following: preterm delivery, fetal chromosomopathies and other anomalies that could affect adaptation to the extrauterine environment, admission of the mother or the newborn to the intensive care unit in the first 48 hours of life, prenatal intention or desire to administer formula feeding, general anesthesia, and having an insufficient understanding of Spanish. Only two mothers (0.3%) refused to participate in the study.

The Ethics and Clinical Research Committee of the Hospital Universitario Puerta de Hierro-Majadahonda approved the study, and informed consent was obtained from all participants before delivery.

The following labor factors were investigated: administration of synthetic oxytocin, mode of delivery, epidural anesthesia, gestational age, and birth weight. In addition, the following sociodemographic factors were recorded at delivery: maternal age, mother's nationality, educational attainment (college degree or not), marital status, parity (primiparous versus multiparous), and prenatal education (maternal education program supported by midwives in primary care). All data were registered by midwives.

For deliveries with a spontaneous onset, exogenous oxytocin was not administered unless the uterine dynamic was poor. Labor was induced with intravenous oxytocin when there was a medical indication to intervene.

To administer oxytocin, a vial of 10 UI (Syntocinon®; Sigma Tau) was diluted in 500 mL of saline solution. It was then given to the patient at a rate of 1 mUI/min, and the dose was doubled every 20 minutes until achieving at least three contractions every 10 minutes. The maximum recommended dose was 32 mUI/min (Cardiff method[11]).

Active management measures were applied in the third phase of labor. After the delivery of the anterior fetal shoulder, 5 UI of oxytocin was administered through a venous catheter. Oxytocin administration was maintained at a rate of 2 UI/h for the first 2 hours of the postpartum period.

In the case of cesarean section, 3 UI of oxytocin was administered through a venous catheter after fetal expulsion, and an additional 10 UI of oxytocin was administered during the first hour of the postpartum period.

When the patient requested epidural anesthesia, an epidural catheter was inserted after receiving informed consent. Anesthesia was induced with either 0.125% levobupivacaine (Normon) plus fentanyl or 0.2% ropivacaine (Inibsa) plus fentanyl.

In the case of vaginal deliveries, when the newborns did not need cardiopulmonary resuscitation, they were dried, identified, and placed in skin-to-skin contact with their mothers for 90 minutes.

After this period, routine measurements were performed (weight, size, cephalic perimeter, eye prophylaxis, and antihemorrhagic prophylaxis). If the newborn had not latched onto the breast spontaneously, both mother and child were oriented to begin breastfeeding.

In the case of cesarean deliveries, when maternal and/or fetal conditions permitted, skin-to-skin contact took place during the surgical procedure and afterward at the postoperative care unit. If skin-to-skin contact was not possible, such contact took place after surgery at the postoperative care unit (in the first 60 minutes of life). Under no circumstances was the newborn placed in a separate room from the mother.

During the stay in the hospital, the nursing staff offered education in breastfeeding, encouraging proper positioning of the newborn to latch onto the mother's breast and answering questions about the process.

Likewise, after discharge from hospital, mothers were able to call a nursing advice line 24 hours a day, 7 days a week, for breastfeeding consultation.

To track the duration of breastfeeding, the use of a pacifier at any time, attendance at a breastfeeding support group, and reintegration into the workplace, telephone calls were made at 3 and 6 months of life.

The study considered EBF at 3 months of life, when the infants had been fed only with mother's own milk, and at 6 months, when they had been fed with mother's own milk with or without the introduction of solid foods (fruits, vegetables, etc.). Partial breastfeeding was considered when the infant was receiving breast milk and formula.

A loss of follow-up was considered after five unsuccessful telephone attempts. After 3 months, 6 participants (1.1%) were considered as dropouts and 17 (3.2%) after 6 months.

Descriptive analyses were performed through absolute and relative frequencies for categorical variables and mean (standard deviation) or median (percentiles 25 and 75) for numerical variables.

Univariate analysis was performed with the chi-square test or with Fisher's exact test for categorical variables.

To identify risk factors associated with the cessation of breastfeeding at 3 and 6 months postpartum, two multivariate logistic regression models were developed. All significant variables in the univariate analysis were entered into the models. The maximum model included cesarean delivery, the absence of a college degree, not having attended a breastfeeding support group, pacifier use, and reintegration into the workplace. A nonautomatic backward procedure was followed to reach the

final model according to the parsimonious principle (criteria to eliminate variables with $p > 0.05$). Goodness of fit was measured by assessing calibration and discrimination models; the Hosmer–Lemeshow test[12] was used to assess calibration and the area under the receiver operating curve was used to assess discrimination.

The statistical significance level was established at 0.05. Statistical analysis was carried out using Stata/IC v.14.1. (StataCorp LP, College Station, TX).[13–15]

Results

The sample characteristics are described in Table 1. The proportion of infants who initiated EBF was 90.4%. At 3 months of life, 64.4% of mothers maintained EBF and this fell to 31.4% at 6 months of life.

Univariate analyses of labor and sociodemographic factors that could be associated with EBF cessation at 3 and 6 months of life are shown in Tables 2 and 3, respectively. Factors influencing the cessation of EBF at 3 months were cesarean delivery, the absence of a college degree, the use of a pacifier, not having attended breastfeeding support groups, and reintegration into the workplace. Factors influencing the cessation of EBF at 6 months were being primiparous, the use of a pacifier, and reintegration into the workplace.

Table 1. Sample Characteristics, *n* (%) or Median (IQR)

Sample characteristics (n = 529)	
Labor factors	
Synthetic oxytocin	294 (55.6)
Cesarean delivery	106 (20)
Planned cesarean (breech presentation, iterative cesarean)	82 (77.4)
Complications during labor	24 (22.6)
Epidural analgesia	488 (92.2)
Gestational age of newborn (weeks), mean (SD)	39.2 (1.1)
Birth weight (grams), mean (SD)	3,276 (400.2)
Sociodemographic factors	
College degree	356 (67.3)
Primiparous	227 (42.9)
Prenatal education	307 (58)
Mother age (years), mean (SD)	33.9 (4.3)
Spanish nationality	465 (87.9)
Partner	524 (99)
Gender of newborn: female	283 (53.5)
Apgar score at 5 minutes	10 (10–10)
Use of a pacifier	376 (71.9)
Use of a pacifier (newborn's age, days), mean (SD)	27.1 (22.2)
BF support group	131 (25)
Reintegration into the workplace	
3 Months	19 (3.6)
6 Months	294 (57.4)
EBF	
3 Months	337 (64.4)
6 Months[a]	161 (31.4)

[a]EBF at 6 months: mothers' own milk with/without solid food.
BF, breastfeeding; EBF, exclusive breastfeeding; IQR, interquartile range.

Table 2. Univariate Analysis of Labor and Sociodemographic Factors According to Cessation/No Cessation of Exclusive Breastfeeding at 3 Months

3 Months of life, n = 523	*EBF,* n *(%)*	*PBF/FF*, n *(%)*	p
Labor factors			
Synthetic oxytocin			
Yes	192 (65.8)	100 (34.2)	0.479
No	145 (62.8)	86 (37.2)	
Mode of delivery			
Vaginal	284 (67.6)	136 (32.4)	0.002
Cesarean	53 (51.5)	50 (48.5)	
Epidural analgesia			
Yes	307 (63.7)	175 (36.3)	0.463
No	28 (73.7)	10 (26.3)	
Sociodemographic factors			
College degree			
No	90 (53.6)	78 (46.4)	<0.001
Yes	247 (69.6)	108 (30.4)	
Parity			
Primiparous	141 (63.2)	82 (36.8)	0.619
Multiparous	196 (65.3)	104 (34.7)	
Prenatal education			
Yes	201 (65.7)	105 (34.3)	0.478
No	136 (62.7)	81 (37.3)	
Gender of newborn			
Male	148 (61.2)	94 (38.8)	0.146
Female	189 (67.3)	92 (32.7)	
Use of a pacifier			
Yes	217 (57.7)	159 (42.3)	<0.001
No	120 (81.6)	27 (18.4)	
BF support group			
Yes	98 (74.8)	33 (25.2)	0.004
No	239 (61)	153 (39)	
Reintegration into the workplace			
Yes	7 (36.8)	12 (63.2)	0.010
No	330 (65.5)	174 (34.5)	

EBF, exclusive breastfeeding; FF, formula feeding; PBF, partial breastfeeding.

The final adjusted model is shown in Table 4. Cesarean delivery, the absence of a college degree, not having attended a breastfeeding support group, and pacifier use were all associated with cessation of EBF at 3 months. Calibration and discrimination were good, with a *p*-value in the Hosmer–Lemeshow test of 0.778 and the area under the receiver operator curve of 0.695.

The candidate variables to predict EBF cessation at 6 months were primiparity, reintegration into the workplace, and the use of a pacifier. All these variables remained significant in the final model (Table 4). Calibration and discrimination were good, with a *p*-value in the Hosmer–Lemeshow test of 0.998 and an area under the receiver-operator curve of 0.748.

Discussion

The present study shows that some labor and sociodemographic factors are associated with premature cessation of EBF; specifically, cesarean delivery, use of a pacifier, not having a college degree, not having attended a breastfeeding

Table 3. Univariate Analysis of Labor and Sociodemographic Factors According to Cessation/No Cessation of Exclusive Breastfeeding at 6 Months

6 Months of life, n = *512*	*EBF,* n *(%)*	*PBF/FF,* n *(%)*	p
Labor factors			
Synthetic oxytocin			
Yes	82 (28.7)	204 (71.3)	0.128
No	79 (35)	147 (65)	
Mode of delivery			
Vaginal	136 (33)	276 (67)	0.118
Cesarean	25 (25)	75 (75)	
Epidural analgesia			
Yes	144 (30.6)	327 (69.4)	0.220
No	15 (39.5)	23 (60.5)	
Sociodemographic factors			
College degree			
No	44 (26.8)	120 (73.2)	0.123
Yes	117 (33.6)	231 (66.4)	
Parity			
Primiparous	53 (24.5)	163 (75.5)	0.004
Multiparous	108 (36.5)	188 (63.5)	
Prenatal education			
Yes	87 (28.9)	214 (71.1)	0.139
No	74 (35.1)	137 (64.9)	
Gender of newborn			
Male	70 (29.7)	166 (70.3)	0.421
Female	91 (33)	185 (67)	
Use of a pacifier			
Yes	89 (24)	282 (76)	<0.001
No	72 (51.1)	69 (48.9)	
BF support group			
Yes	47 (36.4)	82 (63.6)	0.158
No	114 (29.8)	269 (70.2)	
Reintegration into the workplace			
Yes	54 (18.4)	240 (81.6)	<0.001
No	107 (49.1)	111 (50.9)	

EBF, exclusive breastfeeding; FF, formula feeding; PBF, partial breastfeeding.

support group, being primiparous, and reintegration into the workplace.

We noted that EBF at 3 months was lower with cesarean delivery than with vaginal delivery (67.6% and 51.5%, respectively). These data agree with the results published by Oves Suárez et al.,[16] who found an association between vaginal delivery and a higher probability to maintain breastfeeding after 4 months (83.3% versus 16.7% for cesarean delivery). Additionally, a systematic review by Prior et al.,[17] which included 53 studies, and a meta-analysis, including 48 studies, concluded that elective cesarean section was related to low rates of breastfeeding.

Regarding the administration of synthetic oxytocin, a previous study suggests that an active management of the third phase of labor may reduce the rates of breastfeeding at 2 and 6 weeks.[18] Likewise, in a study investigating the relationship between the administration of oxytocin during the first and second phases of labor and initiation and duration of breastfeeding, García-Fortea et al.[19] found a negative association in both the initiation and continuation of breastfeeding at 3 months.

The use of oxytocin during labor and its consequences for breastfeeding is our main field of research. In a preliminary study,[20] we observed that the dose of oxytocin used in mothers who did not maintain EBF at 1 and 3 months of life was higher than that used in mothers who did maintain EBF. However, in a subsequent investigation,[21] we failed to find any relationship between the administration of synthetic oxytocin during labor and the preservation of EBF at 3 and 6 months of life. Our findings in the present study are in agreement with these latter findings.

Epidural analgesia is another labor factor that has been related to breastfeeding. In a systematic review conducted in 2015, which included 23 experimental studies, the authors found that half of the studies reported a negative association between epidural analgesia and breastfeeding.[22] They concluded that more research was needed to obtain meaningful conclusions. In the present work, we found that the rates of EBF at 3 and 6 months were higher in those mothers who did not receive epidural analgesia, but this did not reach statistical significance.

Among the sociodemographic factors related to cessation of breastfeeding, pacifier use has been widely investigated and has been linked to a shorter duration and exclusivity of

Table 4. Multivariate Logistic Regression with Factors Associated with Cessation of Exclusive Breastfeeding at 3 and 6 Months

	Crude ORs (95% CI)	*Adjusted ORs (95% CI)*
Factors at 3 months		
Cesarean delivery	1.98 (1.28–3.07)	2.31 (1.44–3.70)
No college degree	1.98 (1.36–2.89)	2.01 (1.35–3.01)
Use of a pacifier	3.25 (2.04–5.18)	3.85 (2.36–6.28)
Not attending BF support groups	1.90 (1.21–2.96)	1.96 (1.22–3.12)
Reintegration into the workplace	3.25 (1.25–8.40)	—[a]
Factors at 6 months		
Primiparous	1.76 (1.19–2.60)	1.61 (1.05–2.46)
Use of a pacifier	3.30 (2.20–4.96)	3.49 (2.24–5.43)
Reintegration into the workplace	4.28 (2.88–6.37)	4.49 (2.96–6.83)

[a]Reintegration into the workplace was not significant when included in the multivariate model.
BF, breastfeeding; 95% CI, confidence interval; OR, odds ratio.

breastfeeding. After reviewing the evidence, the Breastfeeding Committee of the Spanish Pediatric Association recommended against using a pacifier until breastfeeding was established, usually until after the first month of life.[23] According to Jaafar et al.,[24] the use of a pacifier once breastfeeding has commenced does not affect its prevalence at 4 months of life; however, the authors concluded that not enough information was available about the potential negative consequences of pacifier use in newborns. In the present study, we found a negative relationship between pacifier use and breastfeeding at 3 and 6 months of life. Accordingly, at 3 months, 81.6% of infants who did not use a pacifier maintained EBF compared with 57.7% for those who did. Additionally, at 6 months, 51.1% of infants who did not use a pacifier maintained EBF against 24% who did.

Another factor to consider is the level of education of the mother. According to a study conducted by Machado et al.,[25] mothers with a lower educational level withdrew from EBF more frequently 4 months after labor. Similarly, Jessri et al.[26] studied EBF indicators and found that mothers with a college degree and multiple children had higher rates of EBF after 6 months. Therefore, primiparity might be negatively associated with breastfeeding. The results of our study relate the lack of a college degree to the cessation of EBF at 3 months of life and primiparity to the cessation of EBF at 6 months.

Regarding the attendance at support groups during breastfeeding, we observed that at 3 months of life, the percentage of EBF was 74.8% for mothers who attended a support group compared with 61% for mothers who did not. Similarly, Britton et al.[27] reviewed 34 trials from 14 countries and concluded that the support offered by professionals could help to extend breastfeeding duration, especially during the first 2 months. They also added that personal support was more effective than support over the telephone.

Finally, we found that reintegration into the workplace is related to the duration and exclusivity of breastfeeding. Bai et al.[28] performed a study with 1,738 mothers, finding that only one-third of them maintained breastfeeding after 2 weeks of having returned to the workplace. In our study, reintegration into the workplace was also related to cessation of EBF, both at 3 and 6 months of life; however, at 3 months, only 3.6% of mothers had reintegrated into the workplace, while at 6 months, it was 57.4% of the mothers.

This study has some limitations that must be considered when interpreting the results. The first limitation is one of sample selection bias since all participants expressed their desire to practice breastfeeding before labor and only due date gestations were included. However, we consider it relevant to establish which factors are associated with the abandonment of EBF when mothers were willing to breastfeed, given that they were motivated to begin or maintain breastfeeding. Furthermore, the research took place in a hospital with a BFHI award. These characteristics could minimize the impact of the studied factors over cessation of EBF and reduce its external validity. Additionally, mothers attending breastfeeding support groups may be more predisposed and motivated to breastfeed longer and therefore this may be the reason for the longer duration of breastfeeding in this group. There could be a recall bias that may limit the validity of the study as the information on the type of feeding was retrospectively collected at 3 and 6 months from birth. Nevertheless, there is evidence that this type of questionnaire has high reliability.[29] Loss of follow-up could limit the research findings, but as these were minimal (1.1% and 3.2% in each of the periods studied) and the sample size was suitable, we believe that this did not modify the observed outcomes.

Another limitation to take into account is that EBF at 6 months was considered if the mothers' own milk was provided with or without solid foods. In addition, rates of EBF at 6 months may be influenced by the legislation in force in Spain (16 weeks of maternity leave). Finally, there may be other factors related to cessation of EBF that may have not been analyzed in the present study, such as pre-existing maternal health problems, lifestyle behavior, socioeconomic status, and postnatal depression, among others.

Conclusions

Several risk factors are related to the premature cessation of EBF: cesarean delivery, the use of a pacifier, the lack of a college degree, nonattendance at breastfeeding support groups, being primiparous, and reintegration into the workplace.

Based on these findings, it would be desirable to define strategies to correct the modifiable factors as well as to promote the protective factors with the aim of improving the success rate of maternal breastfeeding to reach the recommendations of the WHO.

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Disclosure Statement

No competing financial interests exist.

References

1. Organización Mundial de la Salud. Alimentación del lactante y del niño pequeño. 2016. Available at www.who.int/mediacentre/factsheets/fs342/es (accessed November 6, 2016).
2. Organización Mundial de la Salud. Lactancia maternal. 2016. Available at www.who.int/topics/breastfeeding/es (accessed November 6, 2016).
3. Pallás CR. Breastfeeding in Spain. A commitment by everyone. *An Pediatr* 2015;83:365–366.
4. Rius JM, Ortuño J, Rivas C, et al. Factores asociados al abandono precoz de la lactancia materna en una región del este de España. *An Pediatr* 2014;80:6–15.
5. Instituto Nacional de Estadística: Encuesta Nacional de Salud. 2013. Available at www.ine.es/jaxi/Datos.htm?path=/t15/p419/a2011/p03/l0/&file=03154.px (accessed November 6, 2016).
6. Bagci AT, Eriksen KG, Sobko T, et al. Breastfeeding practices and policies in WHO European Region Member States. *Public Health Nutr* 2016;19:753–764.
7. Dozier AM, Howard CR, Brownell EA, et al. Labor epidural anesthesia, obstetrics factors and breastfeeding cessation. *Matern Child Health J* 2013;17:689–698.
8. Jonas K, Johansson MB, Nissen E, et al. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. *Breastfeed Med* 2009;4:71–82.

9. Zakarija-Grkovic I, Segvic O, Vuckovic Vukusic A, et al. Predictors of suboptimal breastfeeding: An opportunity for public health interventions. *Eur J Public Health* 2016;26: 282–289.
10. Bonet M, Marchand L, Kaminski M, et al. Breastfeeding duration, social and occupational characteristics of mothers in the French 'EDEN mother-child' cohort. *Matern Child Health J* 2013;17:714–722.
11. Usandizaga JA, De la Fuente P. Tratado de Obstetricia y Ginecología. Madrid: McGraw-Hill-Interamericana, 1997.
12. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Wiley, 2004.
13. Royston P, Moons KG, Altman DG, et al. Prognosis and prognostic research: Developing a prognostic model. *BMJ* 2009;338:b604.
14. Altman DG, Vergouwe Y, Royston P, et al. Prognosis and prognostic research: Validating a prognostic model. *BMJ* 2009;338:b605.
15. Harrell FE Jr. Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer, 2001.
16. Oves Suárez B, Escartín L, Samper MP, et al. Inmigración y factores asociados con la lactancia materna. Estudio CALINA. *An Pediatr* 2014;81:32–38.
17. Prior E, Santhakumaran S, Gale C, et al. Breastfeeding after cesarean delivery: A systematic review and meta-analysis of world literature. *Am J Clin Nutr* 2012;95:1113–1135.
18. Brown A, Jordan S. Active management of the third stage of labor may reduce breastfeeding duration due to pain and physical complications. *Breastfeed Med* 2014;9:494–502.
19. García-Fortea P, González-Mesa E, Blasco M, et al. Oxytocin administered during labor and breast-feeding: A retrospective cohort study. *J Matern Fetal Neonatal Med* 2014;27: 1598–1603.
20. Marín MA, Olza I, Malalana A, et al. Influencia de la oxitocina administrada durante el parto en el mantenimiento de la lactancia materna. Estudio preliminar. *Acta Pediatr Esp* 2012;70:269–271.
21. Fernández-Cañadas A, Marín MA, Olza I, et al. The relationship of the administration of intrapartum synthetic oxytocin and breastfeeding initiation and duration rates. *Breastfeed Med* 2017;12:98–102.
22. French CA, Cong X, Chung KS. Labor epidural analgesia and breastfeeding: A systematic review. *J Hum Lact* 2016; 32:507–520.
23. Lozano MJ, Pallás CR, Hernández MT, et al. Uso del chupete y lactancia materna. *An Pediatr* 2011;74:271.e1–e271.e5.
24. Jaafar SH, Jahanfar S, Angolkarm, et al. Effect of restricted pacifier use in breastfeeding term infants for increasing duration of breastfeeding (Review). *Cochrane Database Syst Rev* 2012:CD007202.
25. Machado MC, Assis KF, Oliveira FC, et al. Determinants of the exclusive breastfeeding abandonment: Psychosocial factors. *Rev Saúde Pública* 2014;48:985–994.
26. Jessri M, Farmer AP, Maximova K, et al. Predictors of exclusive breastfeeding: Observations from the Alberta pregnancy outcomes and nutrition (APrON) study. *BMC Pediatrics* 2013;13:77.
27. Britton C, McCormick FM, Renfrew MJ, et al. Support for breastfeeding mothers (Review). *Cochrane Database Syst Rev* 2007:CD001141.
28. Bai DL, Fong DY, Tarrant M. Factors associated with breastfeeding duration and exclusivity in mothers returning to paid employment postpartum. *Matern Child Health J* 2015;19:990–999.
29. Natland ST, Andersen LF, Nilsen TI, et al. Maternal recall of breastfeeding duration twenty years after delivery. *BMC Med Res Methodol* 2012;12:179.

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APÉNDICE 1. Artículo revista Acta Paediatrica. “Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study”.

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REGULAR ARTICLE

Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study

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ABSTRACT

Aim: To investigate the effect intrapartum oxytocin administration can have on Primitive Neonatal Reflexes. The secondary objective was to observe the influence of intrapartum oxytocin may have on breastfeeding.

Methods: Twenty healthy primiparae with a single gestation at term were included. To assess Primitive Neonatal Reflexes, video film was taken during an experimental situation designed to elicit Primitive Neonatal Reflexes. Three independent observers blinded to the oxytocin dose that had been administered coded the Primitive Neonatal Reflexes. Data regarding breastfeeding were collected by telephone at 3 months.

Results: Medium oxytocin dose was 1931.9 ± 1754.4 mUI. A Kappa index >0.75 was obtained for four Primitive Neonatal Reflexes: swallow, jaw jerk, suck and gazing. A negative association was found between oxytocin dose and sucking ($p = 0.03$). At 3 months of life, women exclusively breastfeeding (63.1%) had received a significantly lower average dose of oxytocin than those not exclusively breastfeeding (36.8%) ($p = 0.04$).

Conclusion: In this pilot study, intrapartum exogenous oxytocin seems to disturb sucking and breastfeeding duration. Further studies are required to confirm these results and to ascertain whether there could be other effects of intrapartum oxytocin on newborn behaviour.

INTRODUCTION

Synthetic oxytocin is the most commonly used drug to induce or augment labour contractions. The assumption that exogenous oxytocin does not cross the placenta and the foetal blood–brain barrier has been questioned (1–3).

Maximal levels of endogenous oxytocin are attained within the first hour following normal undisturbed childbirth in both the maternal and the newborn brain and may be higher when holding the newborn in skin-to-skin contact (4). This increase in oxytocin levels has been related to the existence of a sensitive period with a specific neurohormonal scenario that would assist commencing mother and baby attachment with some similarities to the imprinting observed in other species (5,6).

Several peptide manipulations during the time surrounding birth can alter this specific neurohormonal status both in the mother and in the newborn brain. The consequences of these manipulations remain largely unknown (1). From a neurobiologic perspective, the most frequent manipulations that can affect mother and newborn include labour induction or augmentation with exogenous oxytocin [frequently combined with epidural analgesia (EDA)] and elective caesarean with no prodromal labour. Data from animal research have revealed that perinatal manipulation of the oxytocinergic system in mammals can have lasting effects on attachment, social, feeding and sexual behaviour (1).

Key notes

- A negative association was observed between intrapartum oxytocin dose, newborn sucking and an increased risk of early unwanted breastfeeding discontinuation, which suggests intrapartum oxytocin may reach newborn brain.
- Babies born to women receiving higher doses of intrapartum oxytocin could experience difficulties with some neonatal reflexes related to breastfeeding.
- Further studies are required to confirm these results and ascertain whether there could be other effects of intrapartum oxytocin on newborn behaviour.

Primitive Neonatal Reflexes are a group of inborn unconditioned reflex responses, spontaneous behaviours and reactions to endogenous or environmental stimuli developing during foetal life and observed in all normal healthy term neonates at birth. Some of them have been studied extensively as feeding stimulants (7,8). The impact synthetic oxytocin may have on these Primitive Neonatal Reflexes and on breastfeeding has not been thoroughly researched.

The current study was designed to investigate the effect of intrapartum oxytocin administration can have on Primitive Neonatal Reflexes. The secondary objective was to observe the influence of intrapartum oxytocin may have on breastfeeding. The study hypothesis was that synthetic oxytocin can reach the foetal brain and alter Primitive Neonatal Reflexes involved with breastfeeding likely to be mediated by endogenous oxytocin.

PATIENTS AND METHODS

Inclusion criteria and study design

This prospective study was performed at a Tertiary University Hospital in Madrid between December 2009 and October 2010. Women were requested to participate in the study upon arrival at the delivery room and asked to sign a consent form if they agreed to participate. Inclusion criteria that had to be fulfilled were the following: healthy primiparae (to exclude women with previous breastfeeding experience that could modify breastfeeding duration), with a single gestation at term, no medical problems, wish to breastfeed and correct understanding of language. A newborn Apgar 5 min ≥9 and the mother and the infant being in skin-to-skin contact immediately following the birth for at least 90 min according to maternity practices were also required.

Another inclusion criterion was to receive intrapartum synthetic oxytocin either for labour induction or for augmentation. Routine intravenous administration of oxytocin during labour induction commenced by preparing 10 IU of oxytocin (Syntocinon®, Defiante Farmaceútica, Madeira, Portugal) in 500 mL of 0.9% saline serum. Obstetricians commenced administration of 2 mIU, doubling the dose every 15 min until at least three contractions were attained in 10 min, up to a maximum of 40 mIU. The final dose of intrapartum oxytocin was recorded by midwives assisting the birth. Oxytocin was administered for induction on nine (45%) deliveries and for augmentation on 11 (55%). Each mother received oxytocin postpartum to prevent haemorrhage in the third stage of labour (this dose of oxytocin was not collected).

All mothers requested EDA. In all cases, EDA was performed using 0.125% levobupivacaine (Chirocane®, Abbott, Madrid, Spain) or 0.2% ropivacaine (Naropin® Polybag®, AstraZeneca, Madrid, Spain) associated with fentanyl. Routine administration of fentanyl for EDA commenced with a bolus of 50 mcg and then with an infusion rate of 8–12 mcg/h.

Sociodemographic variables collected were maternal age, educational level, working status at 3 months after the delivery, newborn sex, gestational age and birthweight. The use of pacifier (yes or no and time used) and formula supplement during hospitalization were also recorded (Table 1).

Table 1 Sample characteristics

Sample size	n = 20	100%
Maternal age	31.4 ± 6.4 years	
Educational level		
Primary	2	10
Secondary	6	30
Tertiary	12	60
Not working at 3 months	19	95
Ethnicity		
Caucasian	16	80
Latin American	4	20
Sex (male)	12	60
Gestational age	39.2 ± 1.2 w	
Birth weight	3297.4 ± 251 g	
Pacifier use first month	6	30
Formula supply in hospital	3	15
Age at video	33.6 ± 13.4 h	
Oxytocin dose (mIU)	1931.9 ± 1754.4	

m, months; y, years

The hospital ethics and research committee approved the study.

Experimental procedure and Primitive Neonatal Reflexes filming

Definition for neonatal position and 16 Primitive Neonatal Reflexes observed during the study were predetermined borrowing and building upon those in the neurologic and feeding literature (9). Primitive Neonatal Reflexes included and coded in a binary system (as reached/not reached) were as the following: endogenous reflexes: hand to mouth, finger flex/extend, mouth gape, tongue dart, arm/leg cycle, foot/hand flex; motor reflexes: head lift, head right, head bob/nod, plantar grasp, hand grasp, Babinski toe fan; rhythmic reflexes: suck, jaw jerk, swallow; and antigravity reflex: gazing. Primitive Neonatal Reflexes affecting breastfeeding can be elicited better in a biological nurturing position with the mother in a semireclined position. Then, newborns only dressed with a diaper were placed in skin-to-skin contact while the mothers were lying in a semireclined supine position in a biologic nurturing position (9) (Fig. S1, Supporting information).

To assess Primitive Neonatal Reflexes, a video film was taken during the first 48 h of life. The filming was performed during an experimental situation designed to elicit Primitive Neonatal Reflexes as reported earlier. While making the videotape, the investigators move freely around the room to capture all the reflexes the newborn should make. Breastfeeding practices in our hospital are made upon the recommendations given by the Baby Friendly Initiative. The filming lasted 20 min and was carried out more than 1 h

after the last breastfeeding with the intention to guarantee a seeking behaviour. Mothers were instructed to observe the newborn spontaneous behaviour and not to be proactive for breastfeeding. More specifically, they were told they could talk and/or caress their babies as they wished but they were told not to direct the baby towards the breast or not to put the nipple into the newborn mouth as the study goal was to observe newborn spontaneous behaviour. After the filming, each participant mother received a DVD copy of the film.

Three independent observers blinded to the oxytocin dose that had been administered coded the Primitive Neonatal Reflexes (reach/not reach) by watching the videos. Kappa index of interobserver's agreement was obtained for all 16 Primitive Neonatal Reflexes.

Breastfeeding follow-up

Three months following the birth, all mothers were contacted by telephone and answered some questions regarding breastfeeding. The feeding patterns (exclusive breastfeeding, breastfeeding or formula feeding), use of pacifier and working status were collected. Patients were excluded for the secondary purpose if no contact was obtained after three attempts (n = 1).

Statistical analysis

Results were expressed as mean and standard deviation (SD). The Cohen's kappa was used to measure the agreement between three observers and was expressed with 95% confidence interval. The comparison analysis was made only with Primitive Neonatal Reflexes were Kappa was >0.75. The comparison of two proportions in independent samples was estimated using Fisher's exact test. The Mann–Whitney nonparametric method was used in oxytocin dose two-group comparisons. The box plot was drawn to illustrate the median, quartiles and extreme values of oxytocin doses. The threshold for oxytocin was established with the area under the curve (AUC), and sensitivity and specificity was estimated with confidence intervals (95% CI).All p-values were two-sided and values of 0.05 or less were considered indicative of statistical significance. The SPSS v.14.0 software (SPPS Inc., Chicago, IL, USA) was used to perform all statistical analysis.

RESULTS

Thirty women agreed and signed a consent form to participate in the study. Of those, 10 had to be excluded for different reasons: labour ending in an emergency caesarean (n = 5); newborn requiring hospitalization in the neonatology unit (n = 1), lack of data regarding Oxytocin dose received (n = 1) or because of technical difficulties during the filming of Primitive Neonatal Reflexes (n = 3). One patient was also excluded for the secondary purpose (breastfeeding at 3 months) because she could not be contacted.

The final sample was comprised of 20 mothers and newborn pairs for the primary purpose. Sample demographic characteristics are shown in Table 1. All mothers received EDA and had their labour induced (n = 9) or augmented

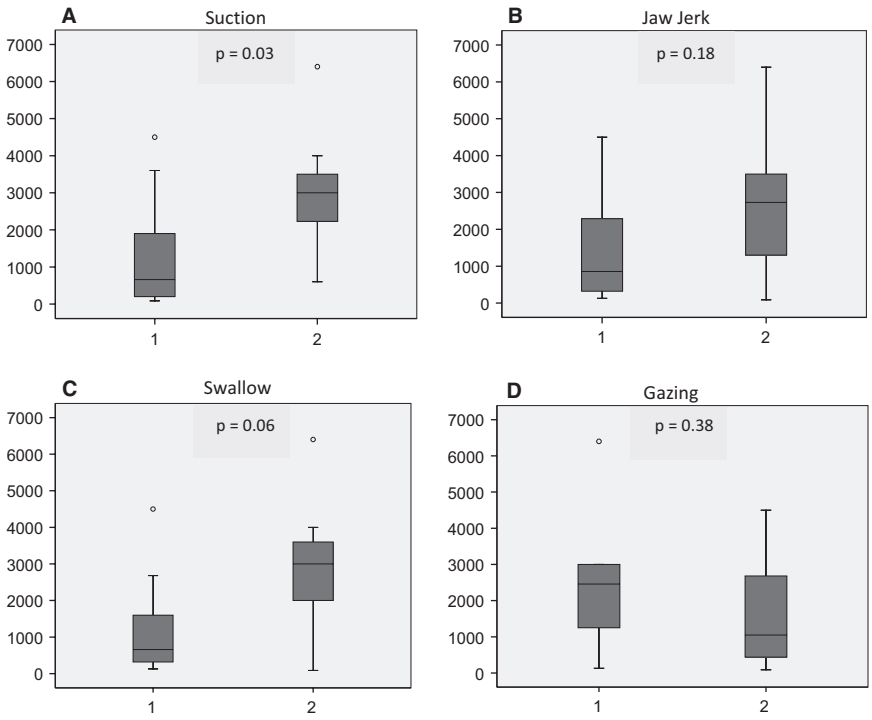

Figure 1 Intrapartum oxytocin dose (mUI) related to the following Primitive Neonatal Reflexes: (A) suction; (B) jaw jerk; (C) swallow; (D) gazing. (n = 20 newborn). 1, observed; 2, not observed.

(n = 11) for different obstetric reasons. The mode of delivery was by forceps in 30%. Mean oxytocin dose received was 1931.9 ± 1754.4 mIU. Duration of delivery was 523.5 ± 173.3 min, and time of rupture of membranes was 767.3 ± 459.4 min. The filming was performed on the second day of newborn life (33.6 ± 13.4 h).

A Kappa >0.75 was obtained only in four items: suck, jaw jerk, swallow and gazing as shown in Table S1 (Supporting information online). According to the function type, the Primitive Neonatal Reflexes affecting breastfeeding can be classified into two categories: (i) those involved with finding the breast and latching and (ii) those involved with milk transfer. Although endogenous reflexes can influence both functions, rhythmic reflexes are considered to only affect milk transfer. The relationship between those four Primitive Neonatal Reflexes and oxytocin dose was performed and results are shown in Figure 1. Mean oxytocin dose where suck was present was 1321.38 ± 1445.01 mIU (median 660 mIU) versus 3065.71 ± 1806.53 mIU (median 3000 mIU) where suck was not observed (p = 0.03). Mean oxytocin dose where swallowing was present was 1226.36 ± 1350.71 mIU (median 660 mIU) versus 2794.22 ± 1873.17 mIU (median 3000 mIU) where swallowing was not observed (p = 0.06).

At 3 months of life, 12 mothers were continuing exclusive breastfeeding (63.1%), two mothers were breastfeeding and supplementing with formula (10.5%), and five were feeding solely on formula (26.3%). Women exclusively breastfeeding had received a lower average dose of oxytocin (1363 ± 1222 mIU) than those women not exclusively breastfeeding at 3 months postpartum (3088 ± 2128 mUI) (p = 0.04). No correlation was found between feeding patterns at 3 months and educational level, use of pacifier or working status.

DISCUSSION

In this small pilot study, intrapartum exogenous oxytocin appears to affect somehow some of the Primitive Neonatal Reflexes involved in breastfeeding as well as breastfeeding duration. Results should be taken with caution but to the best of our knowledge this is the first study that observes such an inhibitory effect of exogenous oxytocin on newborn feeding behaviour. This negative association observed between oxytocin dose and newborn sucking suggests that intrapartum oxytocin may cross both the placenta and newborn blood–brain barrier, producing an effect that can be observed during the second day of life. Although half-life of oxytocin in the circulation is short and only small amounts cross the blood brain barrier, prolong infusion of oxytocin may cause changes in the neuroendocrine environment of the continuous development brain of the newborn (10–12).

It has been suggested that the brain oxytocinergic system plays an important role in the regulation of ingestive behaviours. The role of the oxytocin system in feeding control appears to be related to the induction of satiety responses (13,14). In rats, intracerebroventricular (ICV) injections of oxytocin and oxytocin-R receptor agonists dose-dependently inhibit food and water intake in freely drinking animals and induce thirst in men and women (15–18) and peripheral administration of only high doses of oxytocin generated hypophagia, which strongly suggested that central oxytocin affects feeding (15,16). An inhibitory effect of oxytocin shortly after delivery has been observed in rats, where oxytocin exerts an excitatory-to-inhibitory switch of GABA actions, which seems to protect the foetal brain from birth anoxia (19).

It is tempting to think that the inhibitory effect on sucking (and almost on swallowing) found in our study could be similar to the effect observed in rats following ICV administration of oxytocin. This finding should be replicated and confirmed in future studies but it already raises some important questions. The fact that the effect was observed 24–48 h after the birth leads us to question how long the effect lasts. For example, effects of intrapartum oxytocin infusion are sustained for at least 2 days after the birth and possibly longer on the mother (20). If there is a sensitive period in humans similar to that observed in other animals, as recent evidence suggests, it could be hypothesized that the drugs administered during labour such as exogenous oxytocin that reach the newborn brain can have a long-lasting impact, similar to other routine labour practices (6).

Mothers who continued exclusive breastfeeding 3 months after the birth had received a significantly lower dose of oxytocin than those who were not breastfeeding exclusively. The correlation observed between the intrapartum dose of oxytocin and the early failure of breastfeeding deserves some attention. Prior studies in humans had reported a negative association between intrapartum oxytocin and exclusive breastfeeding duration. In a study performed by Jordan et al. (21), an association between intramuscular oxytocin and formula feeding was stronger when women receiving EDA were excluded, which the authors suggested could be a sign that oxytocin may exert an independent effect. However, the effect had been considered to be mediated by an effect on the mother rather than on the newborn and mediated or related to EDA.

The authors of a previous study had suggested that oxytocin infusion could influence breastfeeding in a positive way because the intrapartum oxytocin dose was associated with lower maternal serum levels of endogenous oxytocin but with higher maternal prolactin levels 2 days following the birth (20). But in other studies, intrapartum oxytocin has also been associated with an increased number of women abandoning breastfeeding (22,23); reduction in the chances to breastfeed within 4 h and increased risk of artificial feeding (24).

Our data suggest that the observed negative relationship between the oxytocin dose and early supplementation or artificial feeding could be related to the inhibitory effect on the newborn rather than by an effect on the mother. Mothers who had received a higher dose of oxytocin were very unlikely to be solely breastfeeding 3 months after the birth and no association was found with other epidemiologic characteristics. However, this is not the primary purpose of the study, so further studies are required to confirm these results.

The main limitation of the current study is the fact that all women received EDA. EDA reduces the release of exogenous oxytocin (25) and is commonly used with synthetic oxytocin. Several reports observed a negative influence on breastfeeding (26,27). Other limitations are the small sample size (so this is a pilot study) and the absence of a control–physiologic group without oxytocin infusion.

There may be other central nervous system effects on the foetus brain that have not yet been researched. Several studies link oxytocin to social behaviours and autism. Excess oxytocin, possibly through oxytocin administration at birth for labour induction, could contribute to the development of autistic spectrum disorders (28). Excess oxytocin has been revealed to reduce bioavailability of oxytocin-R and to down regulate oxytocin-R-mRNA (29). The above information seems to show that in a newborn's brain exposed to oxytocin during labour, oxytocin-R could become, at least temporarily unavailable for further oxytocin binding because of internalization triggered by excess agonist. Primitive Neonatal Reflexes are a group of reflex responses related to attachment and probably, linked to the oxytocin/oxytocin-R system, so the result observed may be accounted for by this adverse effect related to the excess of oxytocin.

The current findings suggest newborn babies born to women receiving higher doses of intrapartum oxytocin could experience difficulties with some neonatal reflexes related to breastfeeding. It was striking to see how some of the babies in the study placed in an ideal biologic nurturing position for 20 min were not at all able to commence breastfeeding spontaneously. Some of those newborns who failed at spontaneous feeding actually spent a significant part of the 20 min of the filming crying, seemingly very frustrated, contrary to the common idea that skin-to-skin contact between mother and newborn has a soothing effect.

To conclude, from these results, intrapartum synthetic oxytocin seems to inhibit sucking that affects breastfeeding. There is an association between intrapartum oxytocin dose and an increased risk of early unwanted breastfeeding discontinuation. Further studies are required to confirm these results and to ascertain whether there could be other effects of intrapartum oxytocin on newborn behaviour.

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DISCLOSURE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

1. Carter CS. Developmental consequences of oxytocin. *Physiol Behav* 2003; 79: 383–97.
2. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. *J Matern Fetal Med* 1996; 5: 245–55.
3. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders? A look at the literature. *Med Hypotheses* 2004; 63: 456–60.
4. Nissen E, Lilja G, Widström AM, Uvnäs-Moberg K. Elevation of oxytocin levels early postpartum in women. *Acta Obstet Gynecol Scand* 1992; 74: 530–3.
5. Klaus M, Kennell J. Parent to infant bonding: setting the record straight. *J Pediatr* 1983; 102: 575–6.
6. Bystrova K, Ivanova V, Edhborg M, Matthiesen AS, Ransjo-Arvidson AB, Mukhamedrakhimov R, et al. Early contact versus separation: effects on mother-infant interaction one year later. *Birth* 2009; 36: 97–109.
7. Touwen BCL. Primitive reflexes–conceptual or semantic problem? In: Prechtl FR, editor. Continuity of neural functions from prenatal to postnatal life. Clinics in dev med Spastics, Internat Medical Publications, London: MacKeith Press; 1984: 115–25.
8. Bu'Lock F, Woolridge MW, Baum JD. Development of co-ordination of sucking, swallowing and breathing: ultrasound study of term and preterm infants. *Dev Med Child Neurol* 1990; 32: 669–78.
9. Colson SD, Meek JH, Hawdon JM. Optimal positions for the release of primitive neonatal reflexes stimulating breastfeeding. *Early Hum Dev* 2008; 84: 441–9.
10. Rydén G, Sjöholm I. Half-life of oxytoxin in blood of pregnant and non-pregnant woman. *Acta Obstet Gynecol Scand* 1969; 48: 139.
11. Ermisch A, Barth T, Rühle HJ, Skopková J, Hrbas P, Landgraf R. On the blood-brain barrier to peptides: accumulation of labelled vasopressin, DesGlyNH2-vasopressin and oxytocin by brain regions. *Endocrinol Exp* 1985; 19: 29–37.
12. Gressens P, Mesples B, Sahir N, Marret S, Sola A. Environmental factors and disturbances of brain development. *Semin Neonatol* 2001; 6: 185–94.
13. Olszewski PK, Klockars A, Schioth HB, Levine AS. Oxytocin as feeding inhibitor: maintaining homeostasis in consummatory behavior. *Pharmacol Biochem Behav* 2010; 97: 47–54.
14. Olszewski PK, Klockars A, Olszewska AM, Fredriksson R, Schioth HB, Levine AS. Molecular, immunohistochemical, and pharmacological evidence of oxytocin's role as inhibitor of carbohydrate but not fat intake. *Endocrinology* 2010; 151: 4736–44.
15. Arletti R, Benelli A, Bertolini A. Oxytocin inhibits food and fluid intake in rats. *Physiol Behav* 1990; 48: 825–30.
16. Benelli A, Bertolini A, Arletti R. Oxytocin-induced inhibition of feeding and drinking: no sexual dimorphism in rats. *Neuropeptides* 1991; 20: 57–62.
17. Olson BR, Drutarosky MD, Chow MS, Hruby VJ, Stricker EM, Verbalis JG. Oxytocin and an oxytocin agonist administered centrally decrease food intake in rats. *Peptides* 1991; 12: 113–8.
18. Olson BR, Drutarosky MD, Stricker EM, Verbalis JG. Brain oxytocin receptor antagonism blunts the effects of anorexigenic treatments in rats: evidence for central oxytocin inhibition of food intake. *Endocrinology* 1991; 129: 785–91.
19. Tyzio R, Cossart R, Khalilov I, Minlebaev M, Hubner CA, Represa A, et al. Maternal oxytocin triggers a transient inhibitory switch in GABA signaling in the fetal brain during delivery. *Science* 2006; 314: 1788–92.

20. Jonas K, Johansson LM, Nissen E, Ejdeback M, Ransjo-Arvidson AB, Uvnas-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. *Breastfeed Med* 2009; 4: 71–82.
21. Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Associations of drugs routinely given in labour with breastfeeding at 48 hours: analysis of the Cardiff Births Survey. *BJOG* 2009; 116: 1622–9.
22. Ounsted MK, Boyd PA, Hendrick AM, Mutch LM, Simons CD, Good FJ. Induction of labour by different methods in primiparous women. II. Neuro-behavioural status of the infants. *Early Hum Dev* 1978; 2: 241–53.
23. Ounsted MK, Hendrick AM, Mutch LM, Calder AA, Good FJ. Induction of labour by different methods in primiparous women. I Some perinatal and postnatal problems. *Early Hum Dev* 1978; 2: 227–39.
24. Wiklund I, Norman M, Uvnas-Moberg K, Ransjo-Arvidson AB, Andolf E. Epidural analgesia: breast-feeding success and related factors. *Midwifery* 2009; 25: e31–8.
25. Rahm VA, Hallgren A, Hogberg H, Hurtig I, Odlind V. Plasma oxytocin levels in women during labor with or without epidural analgesia: a prospective study. *Acta Obstet Gynecol Scand* 2002; 81: 1033–9.
26. Anim-Somuah M, Smyth R, Howell C. Epidural versus non-epidural or no analgesia in labour. *Cochrane Database Syst Rev* 2005; 19: CD000331.
27. Volmanen P, Valanne J, Alahuhta S. Breast-feeding problems after epidural analgesia for labour: a retrospective cohort study of pain, obstetrical procedures and breast-feeding practices. *Int J Obstet Anesth* 2004; 13: 25–9.
28. Hollander E, Cartwright C, Wong C, DeCaria C, Del GuidiceAsch G, Buchsbaum M, et al. A dimensional approach to the autism spectrum. *CNS Spectr* 1998; 3: 22–39.
29. Phaneuf S, Asboth G, Carrasco M, Europe-Finner G, Saji F, Kimura T, et al. The desensitization of oxytocin receptors in human myometrial cells is accompanied by down-regulation of oxytocin receptor messenger RNA. *J Endocrinol* 1997; 154: 7–18.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Experimental filming of primitive neonatal reflexes. Mothers were lying in bed in a semireclined position. Newborns were placed on the motheŕs chest with skin-to-skin contact and then filmed for 20 min.

Table S1 Index of three interobservers' agreement (Kappa) for all 16 Primitive Neonatal Reflexes.

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APÉNDICE 2. Artículo revista Acta Pediátrica Española. “Influencia de la oxitocina administrada durante el parto en el mantenimiento de la lactancia materna. Estudio preliminar”.

ORIGINAL

PEDIÁTRICA

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Influencia de la oxitocina administrada durante el parto en el mantenimiento de la lactancia materna. Estudio preliminar

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Resumen

Introducción: El uso de la oxitocina (Oxt) durante el parto está tan generalizado que hay una tendencia a asumir que sus efectos son bien conocidos. El objetivo del presente estudio es determinar si la Oxt administrada durante el parto posee alguna influencia sobre el mantenimiento de la lactancia materna exclusiva (LME).

Pacientes y métodos: Este trabajo forma parte de un estudio cuyo objetivo principal es valorar la influencia de la Oxt administrada durante el parto en los reflejos neonatales primitivos. Se trata de un estudio descriptivo observacional realizado en 20 díadas madre-hijo. Se incluyeron madres primigestas que no habían presentado complicaciones durante el embarazo y habían tenido un recién nacido a término sano fruto de un parto vaginal inducido o estimulado con Oxt. Se realizó una llamada telefónica a los 3 meses.

Resultados: Las dosis de Oxt que recibieron durante el parto las madres que no mantenían LME al cabo de 1 y 3 meses fueron superiores a las que mantenían LME ($p < 0,05$).

Conclusión: La Oxt administrada durante el parto puede influir de forma negativa en el mantenimiento de la LME.

Palabras clave

Lactancia materna, oxitocina, recién nacido

Abstract

Title: Influence of oxytocin administered during labor in maintaining breastfeeding. Preliminary study.

Introduction: Synthetic oxytocin (Oxt) is the most commonly used drug to induce or augment labour contractions. The objective of the study is to evaluate the effect of Oxt used during labour on exclusive breastfeeding.

Patients and methods: This job is part of an observational descriptive study which primary objective is to investigate the effect of intrapartum oxytocin administration on primitive neonatal reflexes. Twenty women with their first term pregnancies were studied. Inclusion criteria were: healthy primiparae with a single gestation at term and vaginal delivery induced or augmented with Oxt. Three months following the birth all mothers were contacted by telephone to assess feeding.

Results: Women breastfeeding exclusively had received a significantly lower average dose of Oxt than those women who were not exclusively breastfeeding at 1 and 3 months postpartum ($p < 0.05$).

Conclusion: synthetic Oxt used during labour may have negative influence on breastfeeding.

Keywords

Breastfeeding, oxytocin, newborn

Introducción

La oxitocina (Oxt) es un péptido formado por 9 aminoácidos que se sintetiza en los núcleos paraventricular y supraóptico del hipotálamo, y se segrega a la sangre desde las terminaciones axonales de la hipófisis posterior. Tradicionalmente, se conocían sus efectos sobre las contracciones uterinas y en la eyección de leche. Ahora sabemos que la Oxt y la vasopresina cumplen un papel central en la regulación de las conductas sociales, incluidas la conducta sexual, el apego maternoinfantil, la memoria social y el reconocimiento[1-3].

La Oxt sintética se utiliza en un elevado porcentaje de partos, especialmente en mujeres nulíparas[4]. El uso de la Oxt sintética está tan extendido y generalizado que hay una tendencia a asumir que sus efectos son bien conocidos y benignos, e incluso se ha recomendado su uso en dosis mayores para evitar las cesáreas. Sin embargo, se considera que es el fármaco asociado con más frecuencia a efectos adversos prevenibles o evitables durante el parto[5].

Diversos factores pueden influir negativamente en el inicio y el mantenimiento de la lactancia materna (LM), como la falta

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de información prenatal, el bajo nivel educativo, la presencia de problemas en el recién nacido (RN) (p. ej., prematuridad o bajo peso al nacimiento) o los relacionados con el parto (p .ej., cesárea o analgesia epidural)[6,7]. Sin embargo, el efecto que puede tener la administración de Oxt durante el parto sobre la LM no se ha estudiado en profundidad.

El objetivo del presente estudio es determinar si la Oxt administrada durante el parto posee alguna influencia sobre el mantenimiento de la lactancia materna exclusiva (LME).

Pacientes y métodos

Este trabajo forma parte de un estudio cuyo objetivo principal es valorar la influencia de la Oxt administrada durante el parto en los reflejos neonatales primitivos. Se trata de un estudio descriptivo y observacional, llevado a cabo en el Hospital Universitario Puerta de Hierro-Majadahonda. Se incluyó en el estudio a madres primigestas con gestación única, sin ningún tipo de complicación durante el embarazo, que habían tenido un RN a término sano fruto de un parto vaginal inducido o estimulado con Oxt. Además, se consideraron como criterios de inclusión el deseo de administrar LM, el correcto entendimiento del idioma, una puntuación en el test de Apgar del RN a los 5 minutos ≥9 y la firma del consentimiento informado antes del parto. Tras el parto, y según la práctica habitual en nuestro centro, se realizó un contacto piel con piel inmediato de forma ininterrumpida durante los primeros 90 minutos de vida, permitiendo el enganche espontáneo del RN. La muestra del estudio estuvo constituida por 20 díadas madre-hijo. Todas las mujeres recibieron analgesia epidural. El estudio fue aprobado por el comité de ética del centro.

La administración de Oxt durante la inducción del parto se inició preparando 10 UI de Oxt (Syntocinon®, Defiante Farmacéutica) en 500 mL de suero salino al 0,9%. Los obstetras comenzaban administrando 2 mUI, doblando la dosis cada 15 minutos hasta conseguir al menos 3 contracciones en 10 minutos, hasta un máximo de 40 mUI.

La analgesia epidural se aplicó empleando levobupivacaína al 0,125% (Chirocane®, Abbott) asociada a fentanilo, o ropivacaína al 0,2% (Naropin® Polybag®, AstraZeneca) asociada a fentanilo.

Para establecer la duración de la lactancia, dos de los investigadores (I.O. y M.A.) realizaron una llamada telefónica a los 3 meses de edad del lactante, preguntando de forma retrospectiva por el tipo de lactancia establecida al cabo de 1 y 3 meses de edad (LME, LM o lactancia artificial [LA]). Se definió que la lactancia materna era exclusiva si desde el nacimiento el RN sólo había recibido leche materna. Se consideró pérdida para el seguimiento si tras tres intentos de contacto telefónico éste no se conseguía. Una madre no pudo ser localizada, por lo que la muestra del estudio estuvo constituida por 19 madres.

Se recogieron algunas variables epidemiológicas, como la edad de la madre, la nacionalidad, el nivel educacional, el sexo del RN, la edad gestacional, el peso al nacimiento, el empleo de suplementos durante la estancia hospitalaria, el uso del chupete o la incorporación laboral materna.

TABLA 1

Dosis de oxitocina administrada durante el parto según el tipo de lactancia recibida al cabo de 1 y 3 meses de vida

	LME (mUI)	*LM/LA (mUI)*	*p*
1 mes	1.391,2 ± 1.209,6	3.700 ± 2.128,3	0,01
3 meses	1.363,1 ± 1.222,7	3.088,5 ± 2.112,8	0,04

LA: lactancia artificial; LM: lactancia materna; LME: lactancia materna exclusiva.

Los resultados se expresarán como media ± desviación estándar. El test de Shapiro-Wilk se empleó para confirmar la hipótesis de distribución normal. Se empleó el test no paramétrico de Mann-Whitney para la comparación entre grupos. Se consideraron estadísticamente significativos unos valores de $p < 0,05$. Para el análisis estadístico se empleó el programa SPSS v. 14.0 software (SPSS Inc., IL, Estados Unidos).

Resultados

La media de edad de las madres fue de 31,4 ± 6,4 años, la mayoría (89,4%) tenían estudios secundarios o universitarios, eran de nacionalidad española (78,9%) y habían sido amamantadas por sus madres (84,2%). La media de edad gestacional de los RN fue de 39,2 ± 1,2 semanas, y el peso al nacimiento de 3297,4 ± 251 g. El 57,8% eran niños, sólo 3 (15,7%) recibieron suplementos durante el ingreso y tan sólo 5 (26,3%) utilizaban chupete antes del mes de vida. Sólo una madre se incorporó a su trabajo antes de los 3 meses de edad.

Al mes de vida, 14 lactantes (73,7%) recibían LME, 3 (15,8%) LM y 2 (10,5%) LA. A los 3 meses, 12 recibían LME (63,2%), 2 LM (10,5%) y 5 (26,3%) LA. Se observó que las madres que no continuaban con LME al cabo de 1 y 3 meses habían recibido mayores dosis de Oxt durante el parto (tabla 1). No se apreciaron diferencias entre ambos grupos en las diversas variables epidemiológicas consideradas (edad materna, nivel educativo, uso de chupete o de suplementos durante el ingreso).

Discusión

Es posible que la Oxt administrada durante el parto pueda influir de forma negativa en el mantenimiento de la LME.

La Oxt es uno de los fármacos empleados más comúnmente durante el proceso del parto[8]. Inicialmente se consideró que su administración era bastante segura, pues existían dos barreras naturales que evitarían el paso potencial de la Oxt al cerebro del bebé: la barrera maternoplacentaria y la barrera hematoencefálica (BHE) del feto. Sin embargo, Malek et al. estudiaron la difusión madre-feto y feto-madre de Oxt, y encontraron que el transporte es mayor en la primera dirección (madre-feto), es

decir, la Oxt sintética administrada a la madre puede llegar a la circulación fetal[9]. Además, durante el parto se produce una situación de estrés para la madre y el hijo que puede propiciar un aumento de la liberación de citocinas o, lo que es lo mismo, producir un estrés oxidativo que haga que la BHE sea más permeable de lo habitual. En síntesis, es posible que durante el parto la Oxt sintética administrada a la madre pueda pasar dichas barreras y llegar al cerebro del bebé[10].

Recientemente, diversos artículos han lladado la atención acerca de los posibles efectos adversos que puede tener sobre la lactancia la administración de Oxt. Así, Jordan et al., en un estudio realizado en más de 48.000 mujeres, observan que la administración de Oxt se asocia a unas menores tasas de LM a las 48 horas de vida del RN[11]. Asimismo, Wiklund et al., en un trabajo realizado en más de 500 mujeres, aprecian que la Oxt implica un mayor riesgo para un inicio tardío de la LM[12].

El mecanismo por el cual esto puede tener lugar aún no está del todo claro. Por un lado, la Oxt exógena puede interrumpir la secreción pulsátil de Oxt y la actividad subsiguiente de las células mioepiteliales necesaria para el inicio de la lactancia[13,14], alterar las señales en el receptor de Oxt de las células mioepiteliales y endoteliales[15], y alterar el balance de Oxt y los cambios en la arquitectura neuronal en el periodo sensitivo del nacimiento, lo que afectaría a la adaptación maternal[16,17]. En síntesis, la Oxt exógena puede alterar el inicio de la lactancia mediante la alteración de la secreción pulsátil de Oxt y de las oscilaciones de la concentración, por la desensibilización de los receptores y, de manera más especulativa, alterando la conducta infantil o maternal. Sin embargo, queda por determinar cuál es el mecanismo por el que se mantienen estos efectos perjudiciales de la Oxt sobre las fases iniciales de la lactancia, causando una reducción de las tasas de LME en fases posteriores. Es posible que la alteración en la conducta infantil (en los reflejos neonatales encaminados a conseguir una LM adecuada) observada en los periodos iniciales se prolongue en el tiempo y, por tanto, ocasione lactancias menos satisfactorias y una mayor posibilidad de abandono de ésta por parte de las madres. No obstante, sería deseable la realización de más estudios con el fin de confirmar esta hipótesis.

Dentro de las limitaciones de este estudio encontramos que todas las madres recibieron analgesia epidural. No obstante, al ser un efecto presente en toda la muestra, se puede inferir que el efecto observado no se debe únicamente al tipo de analgesia empleado. Al tratarse de un estudio retrospectivo, es posible que la información obtenida a los 3 meses acerca del tipo de alimentación al mes de vida pueda verse modificada por el diseño del estudio. Finalmente, el cálculo del tamaño muestral está realizado en función del objetivo principal del estudio (influencia de la Oxt en los reflejos neonatales primitivos) y, por tanto, es posible que los resultados observados se vieran modificados con un tamaño muestral diferente. Sin embargo, el hecho de que uno de los criterios de inclusión sea el deseo expreso de la madre de proporcionar LM puede ocasionar que se minimice el posible impacto perjudicial que la administración de Oxt puede tener sobre la lactancia.

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Bibliografía

1. Carter CS, Williams JR, Witt DM, Insel TR. Oxytocin and social bonding. Ann NY Acad Sci. 1992; 652: 204-211.
2. Carter CS. Developmental consequences of oxytocin. Physiol Behav. 2003; 79: 383-397.
3. Insel TR, Young LJ. The neurobiology of attachment. Nat Rev Neurosci. 2001; 2: 129-136.
4. Freeman RK, Nageotte M. A protocol for use of oxytocin. Am J Obstet Gynecol. 2007; 197: 445-446.
5. Clark SL, Simpson KR, Knox GE, Garite TJ. Oxytocin: new perspectives on an old drug. Am J Obstet Gynecol. 2009; 200: 35.e1-35.e6.
6. Hernández Aguilar MT, Aguayo Maldonado J; Comité de Lactancia Materna de la Asociación Española de Pediatría. La lactancia materna. Cómo promover y apoyar la lactancia materna en la práctica pediátrica. Recomendaciones del Comité de Lactancia de la AEP. An Pediatr (Barc). 2005; 63: 340-356.
7. Torvaldsen S, Roberts CL, Simpson JM, Thompson JF, Ellwood DA. Intrapartum epidural analgesia and breastfeeding: a prospective cohort study. Int Breastfeed J. 2006; 1: 24.
8. Medication during pregnancy: an intercontinental cooperative study. Collaborative Group on Drug Use in Pregnancy (CGDUP). Int J Gynaecol Obstet. 1992; 39: 185-196.
9. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. J Matern Fetal Med. 1996; 5: 245-255.
10. Wahl RU. Could oxytocin administration during labour contribute to autism and related behavioral disorders? A look at the literature. Med Hypotheses. 2004; 63: 456-460.
11. Jordan S, Emery S, Watkins A, Evans JD, Storey M, Morgan G. Associations of drugs routinely given in labour with breastfeeding at 48 hours: analysis of the Cardiff Births Survey. BJOG. 2009; 116: 1.622-1.629.
12. Wiklund I, Norman M, Uvnäs-Moberg K, Ransjö-Arvidson AB, Andolf E. Epidural analgesia: breast-feeding success and related factors. Midwifery. 2009; 25: e31-e38.
13. Russell JA, Douglas AJ, Ingram CD. Brain preparations for maternity-adaptive changes in behavioral and neuroendocrine systems during pregnancy and lactation. An overview. Prog Brain Res. 2001; 133: 1-38.
14. Nissen E, Uvnas-Moberg K, Svensson K, Stock S, Widstrom AM, Winberg J. Different patterns of oxytocin, prolactin but not cortisol release during breastfeeding in women delivered by caesarean section or by the vaginal route. Early Hum Dev. 1996; 45: 103-118.
15. Reversi A, Cassoni P, Chini B. Oxytocin receptor signaling in myoepithelial and cancer cells. J Mammary Gland Biol Neoplasia. 2005; 10: 221-229.
16. Jonas W, Nissen E, Ransjo-Arvidson AB, Matthiesen AS, Uvnas-Moberg K. Influence of oxytocin or epidural analgesia on personality profile in breastfeeding women: a comparative study. Arch Womens Ment Health. 2008; 11: 335-345.
17. Leng G, Meddle SL, Douglas AJ. Oxytocin and the maternal brain. Curr Opin Pharmacol. 2008; 8: 731-734.

APÉNDICE 3. Artículo revista Breastfeeding Medicine. “Intrapartum synthetic oxytocin reduce the expression of primitive reflexes associated with breastfeeding”.

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Original Article

Intrapartum Synthetic Oxytocin Reduce the Expression of Primitive Reflexes Associated with Breastfeeding

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Abstract

Aim: Several synthetic peptide manipulations during the time surrounding birth can alter the specific neurohormonal status in the newborn brain. This study is aimed at assessing whether intrapartum oxytocin administration has any effect on primitive neonatal reflexes and determining whether such an effect is dose-dependent.

Materials and Methods: A cohort prospective study was conducted at a tertiary hospital. Mother–infant dyads who received intrapartum oxytocin ($n=53$) were compared with mother–infant dyads who did not receive intrapartum oxytocin ($n=45$). Primitive neonatal reflexes (endogenous, antigravity, motor, and rhythmic reflexes) were quantified by analyzing videotaped breastfeeding sessions in a biological nurturing position. Two observers blind to the group assignment and the oxytocin dose analyzed the videotapes and assesed the newborn's state of consciousness according to the Brazelton scale.

Results: The release of all rhythmic reflexes ($p=0.01$), the antigravity reflex ($p=0.04$), and total primitive neonatal reflexes ($p=0.02$) in the group exposed to oxytocin was lower than in the group not exposed to oxytocin. No correlations were observed between the dose of oxytocin administered and the percentage of primitive neonatal reflexes released ($r=0.03$; $p=0.82$).

Conclusions: Intrapartum oxytocin administration might inhibit the expression of several primitive neonatal reflexes associated with breastfeeding. This correlation does not seem to be dose-dependent.

Introduction

Oxytocin has a crucial role in labor (it induces uterine contractions), as well as in the regulation of social behavior including sexual behavior, maternal bonding, and social memory and recognition.[1–4] Synthetic oxytocin is the most commonly used drug to induce or augment labor contractions. Intrapartum oxytocin administration involves the continuous infusion of oxytocin, which results in the inhibition of physiological pulsatility.[5] However, the administration of synthetic oxytocin to induce or increase uterine dynamics is growing. The presence of oxytocin kinases in the placenta and in the brain–blood barrier of the fetus reduces synthetic oxytocin concentrations in the brain of the newborn. However, some synthetic oxytocin concentrations may reach the fetal brain.[6] In mammals, several peptide manipulations during the time surrounding birth may induce persistent changes in the neuroanatomical and neuroendocrine system of the newborn.[7]

Attachment behaviors can be observed immediately after birth. In the period just after birth, human newborns exhibit behaviors aimed at maintaining proximity to the mother and initiating lactation. Skin-to-skin contact between the newborn and the mother facilitates spontaneous latching due, among other factors, to primitive neonatal reflexes (PNRs).[8] PNRs include a group of innate reflexes, spontaneous behaviors, and reactions to endogenous and environmental stimuli. PNRs develop during the fetal period and are observed in all healthy full-term newborns. Some PNRs have been extensively studied, such as the PNR that facilitates breastfeeding.[9] However, the effect of intrapartum hormone manipulation on these reflexes has not been studied until recently.[5,10]

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This study is registered at ClinicalTrials.gov with clinical trial registration number NCT01891201.

This study is aimed at assessing whether intrapartum oxytocin administration has any effect on PNRs and determining whether such effect is dose-dependent.

Materials and Methods

A cohort prospective study conducted at a tertiary hospital. The exposed group included mother–infant dyads who received intrapartum oxytocin ($n=53$). The not exposed group included mother–infant dyads who did not receive intrapartum oxytocin ($n=45$). Inclusion criteria were a single, healthy, full-term newborn delivered by vaginal labor with an Apgar score at 5 minutes of >7, the expressed desire of the mother to breastfeed, and her provision of informed consent. Exclusion criteria were a preterm newborn, a fetal chromosomal or any other type of anomaly diagnosed during gestation that modifies the newborn's adaptation to the extrauterine environment, the transfer of the mother to the intensive care unit, the transfer of the newborn to the intensive care unit within 48 hours after birth, the mother's desire of providing formula feeding expressed before labor, language barriers, and undergoing a cesarean section. Mother–newborn dyads were recruited before delivery. All practices were performed in accordance with the Baby-Friendly Hospital Initiative guidelines: immediately after birth, newborns were placed in skin-to-skin contact during 90 minutes continuously; as well, breastfeeding sessions were conducted at demand, and they were not restricted any time.

This study was approved by the local ethics committee.

The study of PNRs was performed in an experimental maternal skin-to-skin contact situation during the stay at the Maternity Unit (Fig. 1). Parents chose the best moment to videotape the mother and the newborn at least 1 hour after the last feed, in order to favor PNR expression. The mother was positioned in the biological nurturing position[11] (skin-to-skin contact, with the newborn only dressed with a diaper facing, touching and in close apposition with the interbreast zone of the mother at a 30–64° angle). The mother was asked not to induce the newborn to seek or latch, although she was allowed to touch or speak to him or her. One of the researchers (I.O.F., M.A.M.G., or C.G.A.) videotaped the situation for 15 minutes. Parents were provided with a CD with the recordings as a gift.

Next, two observers blind to the group assignment and the oxytocin dose administered analyzed the videotapes and assessed the newborn's state of consciousness at the start of the recording, according to the Brazelton scale,[12] and scored the PNRs using a dichotomous code (achieved/not achieved).

The 15 PNRs evaluated were as follows: (1) endogenous reflexes—hand to mouth, finger flexion and extension, mouth gape, tongue dart, arm/leg cycle, and foot/hand flex; (2) antigravity reflex—gazing; (3) motor reflexes—head turning, bobbing, plantar grasp, and Babinski toe fan; and (4) rhythmic reflexes—suck, jaw jerk, and swallowing.

The intraclass correlation coefficient was obtained for all 15 PNRs. The value of the intraclass correlation coefficient was as follows: (1) endogenous reflexes, 0.73 (0.59–0.83); (2) antigravity reflex, 0.70 (0.54–0.80); (3) motor reflexes, 0.74 (0.61–0.83); (4) rhythmic reflexes, 0.95 (0.93–0.97); and (5) and total PNRs, 0.83 (0.73–0.88).

Demographic data, such as educational level, previous deliveries, civil status, delivery mode (instrumental or not), sex of the newborn, Apgar score, gestational age, and weight of the newborn, among other parameters, were collected. Eutocic delivery was considered if no instrument (such as forceps or vacuum) was used during vaginal delivery.

Oxytocin administration during labor induction was performed as indicated by the obstetrician in accordance with the Cardiff protocol: infusion of 10 units of oxytocin (Syntocinon®; Defiante Farmaceutica, Funchal, Portugal) added to a 500-mL bag of physiologic saline (0.9% NaCl) solution. Administration of 2 mIU was initiated, and the dose was doubled every 15 minutes until at least three contractions were achieved in 10 minutes, up to a maximum of 40 mIU. The final dose of oxytocin administered was recorded by the midwives conducting the delivery. All mothers received oxytocin after the delivery for preventing bleeding in the third stage of the labor.

Epidural analgesia was induced with 0.125% levobupivacaine (Chirocane®; Abbott, Abbott Park, IL) or 0.2% ropivacaine (Naropin® Polybag®; AstraZeneca, London, United Kingdom) in conjunction with fentanyl. As many as 95.6% of the women exposed to oxytocin received epidural analgesia, versus 26.8% of the women in the control group.

FIG. 1. Experimental maternal skin-to-skin contact situation.

Statistical analysis

Accepting an alpha risk of 0.05 and a beta risk of 0.20 in a bilateral contrast, the sample size necessary was 90 subjects (45 in each group) for detecting a difference of ≥ 10 percentage units. The common standard deviation was assumed to be 20. We calculated a lost to follow-up rate of 0.05.

Results are expressed as mean ± standard deviation or median (interquartile range). Qualitative variables are presented as absolute frequency values and percentage values. The hypothesis of normal distribution was confirmed by the Shapiro–Wilk test. Differences between groups were assessed by Student's *t* test and the nonparametric Mann–Whitney U test. The association between oxytocin and neonatal reflexes was determined through Pearson's correlation coefficient. Qualitative variables were analyzed by the chi-squared test using Yates–Fisher correlation coefficients, when necessary. A multiple regression analysis was performed to study the variables that could modify the expression of PNRs. The intraclass correlation coefficient is a measurement of agreement between observers. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed using SPSS version 14.0 software (SPSS Inc., Chicago, IL).

Results

In total, 98 mother–newborn dyads were initially included in the study, of which 53 were included in the group exposed to oxytocin and 45 were assigned to the not exposed group. Eight patients (15%) of the exposed group were excluded for the following reasons: four patients were excluded for technical reasons, two for missing data, and two for refusal to continuing after having provided initial consent. Four patients (8.8%) were excluded from the not exposed group: one was excluded for technical problems, and three were excluded for medical reasons (broken collarbone, gastric lavage, and admission to phototherapy, respectively).

The final sample included 86 mother–infant dyads, of which 45 were exposed to oxytocin and 41 were not exposed. Epidemiologic characteristics are shown in Table 1. The women exposed to oxytocin were more likely to be primiparous, receive epidural analgesia, and record earlier and require the use of instrumental aid during labor, compared with the not exposed group. The median dose of oxytocin was 1,400 units (range, 340–4,460 mU).

PNRs

The release of all the rhythmic reflexes, the gravity reflex, and total PNRs in the group exposed to oxytocin was lower compared with that in the not exposed group (Table 2).

No differences were found in the state of consciousness of the newborn on initiation of the experimental situation of biological nurturing. No differences were found in the percentage of endogenous reflexes released or in the percentage of motor reflexes.

A multiple regression analysis was performed to study if the different epidemiological characteristics between groups (multiparous, eutocic delivery, epidural analgesia, time at videotaping, and group) could modify the expression of PNRs. No significant differences in any of the analyzed variables were observed except in the treatment group ($p = 0.04$) (Table 3).

Table 1. Epidemiologic Characteristics

	Oxytocin group	*Control group*	p
Mother's education			0.79
Primary	2.3%	2.5%	
Secondary	31.8%	35%	
University	65.9%	62.5%	
Multiparous	40%	73.2%	0.004
Eutocic delivery	77.8%	100%	0.01
Epidural analgesia	100%	26.8%	< 0.001
Newborn's sex (male)	46.7%	48.8%	0.81
Gestational age (weeks)	39.7 ± 1.1	39.2 ± 1.2	0.17
Newborn's weight (g)	3,324 ± 375	3,240 ± 476	1
Apgar score at 5 minutes	10 (10–10)	10 (10–10)	1
Not requiring resuscitation	77.8%	85.4%	0.57
Time after birth (hours)	23.4 ± 11.2	30.8 ± 8.2	0.001

Data are expressed as percentages, in mean ± standard deviation or median values (interquartile range), as indicated.

Correlation with the dose of oxytocin administered

No correlations were observed between the dose of oxytocin administered and the percentage of PNRs released ($r = 0.03$; $p = 0.82$).

Discussion

The results obtained in this study suggest that intrapartum oxytocin administration may influence the expression of primitive reflexes favoring breastfeeding initiation. Specifically, the administration of oxytocin was observed to have higher impact on antigravity and rhythmic reflexes, with the latter being associated with effective breastfeeding. However, these results should be carefully considered.

The results observed are consistent with those of a previous study conducted by our group[10]; indeed, a slightly higher correlation has been observed in our study. Also, Bell et al.[5] in

Table 2. State of Consciousness and Percentage of Primitive Neonatal Reflex Expression in the Oxytocin and Control Groups

	Oxytocin group	*Control group*	p
Brazelton scale[a]			0.16
1–3	36.6%	17.1%	
4–5	41.5%	58.5%	
6	22%	24.4%	
PNR			
Endogenous reflexes (%)	67.2 ± 31.3	79.7 ± 24.1	0.08
Motor reflexes (%)	66.6 ± 36.1	82.3 ± 26.9	0.06
Rhythmic reflexes achieved	17.8%	43.9%	0.01
Antigravity reflexes achieved	73.3%	90.2%	0.04
Total PNR (%)	58.4 ± 28.9	74.1 ± 25.4	0.02

Results are expressed as mean ± standard deviation values.
[a]Brazelton scores are as follows: 1, deep sleeping; 2, active sleeping; 3, sleepiness; 4, alert when awake; 5, unrestlessly alert; and 6, crying.
PNR, primitive neonatal reflexes.

Table 3. Multiple Regression Analysis to Study the Variables That Could Modify the Expression of Primitive Neonatal Reflexes

	β	95% CI	p
Multiparous	−4.02	(−17.3, 9.2)	0.54
Eutocic delivery	16.8	(−1.3, 35.1)	0.07
Epidural analgesia	−6.1	(−21.9, 9.6)	0.44
Time of videotaping	0.4	(−0.1, 1)	0.18
Group	−12.7	(−25, −0.5)	0.04

Results are expressed as β coefficients and 95% confidence intervals (CIs).

a study with 47 healthy full-term infants (36 exposed and 11 not exposed to intrapartum synthetic oxytocin) described fewer prefeeding cues in infants exposed versus not exposed to intrapartum oxytocin. Oxytocin administration during labor has some impact on both onset and duration of breastfeeding, as reported by García Fortea et al.[13] In a retrospective cohort study they found an increased risk of bottle feeding and also an increased risk of breastfeeding withdrawal at 3 months in those exposed to intrapartum oxytocin.

The negative association found between intrapartum oxytocin administration and PNRs suggests that oxytocin can cross the placental barrier and the fetal brain–blood barrier, thus causing an effect that can still be observed in the newborn during the first days of life. It has also been observed that this effect is not dose-dependent, most likely because of the mean lifetime of oxytocin.[14] However, the continuous infusion of oxytocin inhibits the physiologic pulsatile release of oxytocin. This may induce changes in the neuroendocrine environment of the fetal nervous system, with potential effects on the neural development of the newborn that can be determined in an objective manner, at least in the short term.[15]

There are several oxytocin receptors areas in the central nervous system, including the nucleus accumbens, the amygdala, the hippocampus, or the spinal cord, among others.[16] The increased density of oxytocin receptors in these areas is associated with a greater bonding and social behavior.[17] Oxytocin administered at low doses favors memory, social learning, and maternal behaviors.[18] However, when administered at high doses, oxytocin may interfere in social memory. In fact, some authors have suggested a relationship between the current tendency to increase oxytocin doses and the increase in the incidence of autism[19] and attention deficit hyperactivity disorder.[20] The triggering mechanism seems to be associated with a desensitization of the oxytocin receptor system.[21] Gimpl and Fahrenholz[22] observed that after stimulating the oxytocin receptor with agonists for 5–10 minutes, oxytocin was internalized within the cell and was not restored to the membrane surface. Excessive administration of oxytocin has also been observed to reduce oxytocin receptor mRNA synthesis and, consequently, oxytocin receptor availability.[23] Thus, intrapartum oxytocin administration may reduce the expression of PNRs as a result of its effects on several areas of the central nervous system of the newborn. In consequence, administering oxytocin during labor may reduce the expression of the oxytocin receptor or cause its desensitization.

The Epigenetic Impact of Childbirth hypothesis suggests that intrapartum oxytocin manipulation may lead to fetal epigenomic remodeling anomalies leading to abnormal gene expression that could cause in a range of noncommunicative diseases and biobehavioral problems in the neonate and adulthood unknown up to date.[24]

Studies in rodents have shown how perinatal manipulations with either synthetic oxytocin or an oxytocin antagonist have long-term behavioral consequences such as inhibited parental behavior or altered capacity to form pair bonds in adulthood.[25,26]

The oxytocinergic system is also related with the regulation of aspects such as food intake and satiety.[27,28] Studies performed on rats have revealed that the intracerebroventricular administration of oxytocin inhibits food and water intake, thus suggesting that oxytocin is involved in the regulation of feeding.[29] This might lead us to think that the inhibitory effects of oxytocin administered during labor on PNRs—especially on the rhythmic reflexes of sucking, jaw jerk, and swallowing, which involve the correct transfer of food—are similar to the anorectic effects of administering intracerebroventricular oxytocin to animals.

Theoretically, there are two barriers impeding the flow of oxytocin into the brain of the newborn: the placental barrier and the brain–blood barrier. On the one hand, the placental barrier contains oxytocinases involved in the degradation of oxytocin.[30] However, studies have demonstrated that despite the existence of these enzymes, small quantities of oxytocin reach the fetal bloodstream.[6] On the other hand, the brain–blood barrier considerably inhibits the passage of peptides such as oxytocin. However, during the fetal stage, this barrier is not entirely mature, and a range of factors may increase its permeability[31,32] (stress, infections, etc.), thus allowing the flow of oxytocin into the brain of the newborn.

There are several limitations to this study. First, the epidemiologic characteristics of both groups are not homogeneous because the control group included more multiparous women. As multiparous women have previous experience in breastfeeding and caring for a newborn, when they are positioned in the biological nurturing position, they may make reflex movements favoring PNR expression. Similarly, the group of patients exposed to oxytocin was more likely to receive epidural analgesia. The administration of epidural analgesia reduces the release of endogenous oxytocin,[33] which might influence PNR expression. However, both factors were not observed in this study to have any influence on PNR expression. The videotaping occurred earlier in the oxytocin-exposed group, and it may reflect a different state of awakeness, but there were no differences on the Brazelton scale or on PNRs. Traditionally, the main difference in the state of consciousness is between the first 6 hours (usually a state of alert) after delivery and beyond. Time of recording was done when both newborn groups were more than 6 hours old. Our hospital works according to the Baby-Friendly Hospital Initiative guidelines, so it is possible that the effects on breastfeeding may be undervalued. According to the power calculation 45 mother–newborn dyads were required in each group, but the nonexposed group had 41 dyads. This may influence the results.

Conclusions

Intrapartum oxytocin administration may inhibit the expression of several PNRs associated with breastfeeding. However, this correlation does not seem to be dose-dependent.

Further studies are necessary to confirm the results obtained in this study and to investigate the potential effects of oxytocin on breastfeeding or on the behavior of the newborn.

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Disclosure Statement

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References

1. Carter CS. Developmental consequences of oxytocin. *Physiol Behav* 2003;79:383–397.
2. Insel TR, Young LJ. The neurobiology of attachment. *Nat Rev Neurosci* 2001;2:129–136.
3. Baumgartner T, Heinrichs M, Vonlanthen A, et al. Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron* 2008;58:639–650.
4. Olza-Fernández I, Marín Gabriel MA, Gil-Sanchez A, et al. Neuroendocrinology of childbirth and mother-child attachment: The basis of an etiopathogenic model of perinatal neurobiological disorders. *Front Neuroendocrinol* 2014;35: 459–472.
5. Bell AF, White-Traut R, Rankin K. Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth. *Early Hum Dev* 2012;89:137–143.
6. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. *J Matern Fetal Med* 1996;5:245–255.
7. Bales KL, Lewis-Reese AD, Pfeifer LA, et al. Early experience affects the traits of monogamy in a sexually dimorphic manner. *Dev Psychobiol* 2007;49:335–342.
8. Widstrom AM, Ransjo-Arvidson AB, Matthiesen AS, et al. Gastric suction in healthy newborn infants. *Acta Paediatr Scand* 1987;76:566–572.
9. Bu'Lock F, Woolridge MW, Baum JD. Development of coordination of sucking, swallowing and breathing: Ultrasound study of term and preterm infants. *Dev Med Infant Neurol* 1990;32:669–678.
10. Olza Fernández I, Marín Gabriel MA, Malalana Martínez A, et al. Newborn feeding behaviour depressed by intrapartum oxytocin: A pilot study. *Acta Paediatr* 2012;101:749–754.
11. Colson SD, Meek JH, Hawdon JM. Optimal positions for the release of primitive neonatal reflexes stimulating breastfeeding. *Early Hum Dev* 2008;84:441–449.
12. Brazelton TB, Nugent JK. *Neonatal Behavioral Assessment Scale*, 3rd ed. MacKeith Press, London, 1995.
13. García Fortea P, González Mesa E, Blasco M, et al. Oxytocin administered during labor and breast-feeding: A retrospective cohort study. *J Matern Fetal Neonatal Med* 2014;27:1598–1603.
14. Rowland M, Tozer TN. Why clinical pharmacokinetics? In: *Clinical Pharmacokinetics: Concepts and Applications*, 3rd ed. Lippincott Williams and Wilkins, Philadelphia, 1995, pp. 1–10.
15. Rydén G, Sjöholm I. Half-life of oxytocin in blood of pregnant and non-pregnant women. *Acta Obstet Gynecol Scand* 1969;48(Suppl 3):139+.
16. Feldman R. Oxytocin and social affiliation in humans. *Horm Behav* 2012;61:380–391.
17. Francis DD, Champagne FC, Meaney MJ. Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. *J Neuroendocrinol* 2000;12: 1145–1148.
18. Klenerova V, Krejci I, Sida P, et al. Oxytocin and carbetocin effects on spontaneous behavior of male rats: Modulation by oxytocin receptor antagonists. *Neuro Endocrinol Lett* 2009;30:335–342.
19. Hollander E, Cartwright C, Wong C, et al. A dimensional approach to the autism spectrum. *CNS Spectrums* 1998;3:22–39.
20. Kurth L, Haussmann R. Perinatal pitocin as an early ADHD biomarker: Neurodevelpmental risk? *J Atten Disord* 2011;15: 423–431.
21. Robinson C, Schumann R, Zhang P, et al. Oxytocin-induced desensitization of the oxytocin receptor. *Am J Obstet Gynecol* 2003;188:497–502.
22. Gimpl G, Fahrenholz F. The oxytocin receptor system: Structure, function and regulation. *Physiol Rev* 2001;81:642–643.
23. Phaneuf S, Asboth G, Carrasco M, et al. The desensitization of oxytocin receptors in human myometrial cells is accompanied by downregulation of oxytocin receptor messenger RNA. *J Endocrinol* 1997;154:7–18.
24. Dahlen HG, Kennedy HP, Anderson CM, et al. The EPIIC hypothesis: Intrapartum effects on the neonatal epigenome and consequent health outcomes. *Med Hypotheses* 2013;80: 656–662.
25. Bales KL, Pfeifer LA, Carter CS. Sex differences and developmental effects of manipulations of oxytocin on alloparenting and anxiety in prairie voles. *Dev Psychobiol* 2004;44:123–131.
26. Bales KL, van Westerhuyzen JA, Lewis-Reese AD, et al. Oxytocin has dose-dependent developmental effects on pair-bonding and alloparental care in female prairie voles. *Horm Behav* 2007;52:274–279.
27. Olszewski PK, Klockars A, Olszewska AM, et al. Molecular, immunohistochemical, and pharmacological evidence of oxytocin's role as inhibitor of carbohydrate but not fat intake. *Endocrinology* 2010;151:4736–4744.
28. Olszewski PK, Klockars A, Schioth HB, et al. Oxytocin as feeding inhibitor: Maintaining homeostasis in consummatory behaviour. *Pharmacol Biochem Behav* 2010;97:47–54.
29. Arletti R, Benelli A, Bertolini A. Oxytocin inhibits food and fluid intake in rats. *Physiol Behav* 1990;48:825–830.
30. Patient C, Davison J, Charlton L, et al. The effect of labour and maternal oxytocin infusion on fetal plasma oxytocin concentration. *Br J Obstet Gynaecol* 1999;106:1311–1313.
31. Agnagnostakis D, Messaritakis J, Damianos D, et al. Blood-brain barrier permeability in healthy infected and stressed neonates. *J Pediatr* 1992;121:291–294.
32. Noseworthy M, Bray T. Effect of oxidative stress on brain damage detected by MRI and in vivo ^{31}P-NMR. *Free Radic Biol Med* 1998;24:942–951.
33. Rahm VA, Hallgren A, Hogberg H, et al. Plasma oxytocin levels in women during labor with or without epidural analgesia: A prospective study. *Acta Obstet Gynecol Scand* 2002;81:1033–1039.

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