Alimentación con Leche Humana exclusiva para infantes prematuros

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RESUMEN

La leche humana no sólo provee la nutrición ideal para el desarrollo del bebé sino también factores inmunológicos para proteger de la infección y la inflamación. Para el infante pretérmino recién nacido, la forma natural de lactancia no es posible, y en cambio, leche materna extraída, leche humana de donante, y fortificación de leche humana, son las bases del cuidado clínico. La investigación actual demuestra riesgo disminuido de ECN con leche materna o leche humana donada cuando se compara individualmente con fórmula y con una dieta de leche humana completa con leche materna suplementada con leche humana de banco. La incidencia de retinopatía de prematuro severa disminuye con alimentación con leche humana exclusiva, y este descenso es más pronunciado con fortificador de leche basado en leche humana comparado con el basado en leche bovina. La incidencia de otras morbilidades tales como sepsis tardía y displasia broncopulmonar es disminuida con mayor dosis de leche humana pese a que no son aparentes diferencias significativas en los estudios de alimentación con leche humana exclusiva.

Palabras claves: Leche humana

Infante pretérmino

Crecimiento

Nutrición

Introducción

El nacimiento muy prematuro (MPT) está asociado a riesgos aumentados de morbilidad y mortalidad. A medida que los científicos investigaron métodos para mejorar la tasa de sobrevida libre de morbilidad en esta población, el tipo de alimentación, específicamente leche humana (LH) versus fórmula, fue descubierto como un método potencial de favorecer los resultados del infante muy pretérmino. Sin embargo, el estudio de este efecto ha sido restringido debido a dificultades inherentes a la conducción del estudio. La provisión de leche materna el infante depende de la habilidad de la madre para extraerse leche y, desafortunadamente, los métodos para optimizar la iniciación y continuación de extracción

de leche, aunque mejorando, no son adecuados para todas las madres y, por lo tanto, no permiten la randomización para leche materna. La alimentación con leche humana donada (LHD) requiere eliminación de la contaminación bacteriana, por pasteurización según la literatura actual de resultados en LH, lo cual disminuye tanto los componentes nutricionales como el efecto inmunitario de LH. Adicionalmente, los déficits nutricionales tanto con leche materna y especialmente con LHD responden positivamente a la suplementación con fortificador de leche humana (FLH). Con la asociación entre crecimiento del infante prematuro y neurodesarrollo, esta suplementación puede ser crítica para optimizar los resultados del infante pretérmino positivamente asociados a la trayectoria del crecimiento. Además, un FLH basado en LH está ahora disponible en algunos mercados y ha recisado la definición de una "dieta con leche humana exclusiva" para incluir la leche materna, LHD, y FLH basado en LH. Sin embargo, la disponibilidad del FLH-basado en LH no es universal, y su elevado costo financiero debe ser confrontado con la consideración de su efectividad. Por lo tanto, FLH- basado en leche bovina o NO fortificación son prácticas comunes en todo el mundo. Todos estos factores complican la investigación sobre el beneficio de la dieta exclusiva con LH para infantes prematuros. Pese a esto, numerosos estudios sobre LH, observacionales, ensayos clínicos, y meta-análisis proveen evidencia de que es el mejor método para alimentar a un infante prematuro.

Función de la leche materna

La leche materna (LM) es el alimento ideal para los bebés. Algunos componentes pueden variar según la dieta materna, y los alimentos complementarios son indicados en la segunda mitad del primer año, pero, en general, es el gold standard al que se deben comparar todos los otros tipos de alimentación. Las necesidades nutricionales de un infante pretérmino varían levemente de aquéllas de las de un infante pretérmino dado que el aporte de ciertos nutrientes es superior para un feto que para el recién nacido. Cuando el infante prematuro pierde la nutrición fetal, se acumulan déficits, y puede requerir mejoras con suplementación de nutrientes.

La función de la LM va mucho más allá del soporte nutricional para el infante dado que provee soporte inmune y promueve el desarrollo de órganos. El desarrollo del intestino está sostenido primero por el líquido amniótico que entrega factores de crecimiento tales como factor de crecimiento epidérmico, hormona de crecimiento, factor transformador del crecimiento alpha y beta, eritropoyetina, y factor de crecimiento tipo insulina que se saben relacionados con el desarrollo de vellosidades en el feto. Estas mismas hormonas y otras, como glutamina y factor estimulante de colonias de granulocitos, están en la LH y afectan la maduración y diferenciación del sistema gastrointestinal a lo largo de la infancia (1). Adicionalmente, las células germinales que demuestran pluripotencialidad han sido aisladas

de la LH y pueden jugar un rol en el desarrollo epitelial de la pared (2). En estudios clínicos, la exposición a LM está asociada con permeabilidad intestinal disminuida, y, por lo tanto, maduración intestinal aumentada, tanto para infantes pretérmino como a término (3, 4).

La LM también tiene un rol crítico en la promoción de la función inmune temprana. Se ha mostrado en estudios animales que leucocitos activos, predominantemente los macrófagos del calostro, pasan a través del epitelio intestinal hacia la circulación del infante (5, 6). La función adaptativa inmune es transmitida de la madre al infante por la IgA secretoria (IgAs) que proporciona protección a corto y largo plazo al intestino a través de la regulación de la microbiota intestinal y de la expresión de genes intestinales (7). Aún elementos nutricionales de la LM sostienen la función inmune garantizando la descripción "componentes multifuncionales de la leche". Por ejemplo, lactoferrina es quelante del hierro libre y es pensado que sostiene la absorción de hierro del infante y quizás tiene un efecto antibacteriano disminuyendo el hierro libre disponible para las bacterias. Aún, ahora se sabe que esta glicoproteína tiene un efecto directo de estimulación de la fagocitosis por macrófagos e inhibe bacterias, virus, y hongos a través de este mecanismo y potencialmente otros (8, 9). Otro ejemplo es el producto de triglicéridos, monoglicérido, que actúa como detergente de las membranas de los patógenos (9). Estos componentes multifuncionales de la leche son constituyentes críticos de la función inmune innata proporcionada por la LM. Citoquinas anti y pro-inflamatorias, bloqueadores de receptores de citoquinas pro-inflamatorias, hormonas como la adiponectina, y los oligosacáridos de la LH son otros ejemplos de los muchos y diversos elementos que brindan protección inmune de la madre al niño (1, 10, 11).

Resultados de nutrición con LM en infantes prematuros

Estudios in vitro y mecanicistas de LM muestran función en el desarrollo e inmunológica, pero ¿cómo afectan estos procesos el resultado clínico? Desafortunadamente, el nivel máximo de evidencia de un estudio clínico-el ensayo cegado, randomizado, controlado- no es una opción porque los infantes no pueden ser randomizados para recibir o no recibir LM. Por lo tanto, los resultados son mejor examinados a través de estudios de cohorte prospectivos y meta-análisis de estos estudios. La publicación en Lancet de Lucas y Cole de 1990 de un estudio prospectivo multicéntrico de 926 infantes prematuros demostró una disminución en ECN con alimentación con LM y con LHD pasteurizada comparada con fórmula. Encontraron que una dieta exclusiva de LH era lo más efectivo y el beneficio se mantenía con la ingesta de cualquier cantidad de LH comparada con sólo fórmula (12). Este trabajo fue seguido de tres estudios de cohorte prospectivos enfocados en los primeros resultados de infantes MPT alimentados con LM. Debe notarse que, en estos tres estudios, LM fue fortificada con FLH en base a leche de vaca a 100 ml/kg/d. En el primer estudio, 108

infantes prematuros alimentados al menos con 50 ml/kg/d LM fueron comparados con infantes prematuros alimentados exclusivamente con fórmula. Los infantes alimentados con esta proporción de LHF exhibieron menos ECN, menos sepsis tardía, y una estadía hospitalaria significativamente más corta (13). En el segundo estudio, 119 infantes MBPN fueron comparados según recibieran No LM o 1-24, 25-49, o ≥50 ml/kg/d en el primer mes postnatal. Al igual que en el estudio anterior, encontraron significativamente menos episodios de sepsis con ≥50 ml/kg/d. No encontraron diferencia significativa en ECN como se vio anteriormente (14). En el tercer estudio, en lugar de medir ml/kg/d de LM, la comparación fue <50% o ≥50% en los primeros 14 días postnatales. En 202 infantes MBPN, el riesgo de ECN fue significativamente más bajo en los infantes que recibieron ≥50% de sus raciones en LM (15). Se cree también que la LM no sólo tiene efecto sobre el desarrollo intestinal sino sobre el desarrollo del cerebro. El efecto potencial de la ingesta de LM sobre el neurodesarrollo del infante pretérmino fue evaluado en las bases de datos de dos estudios grandes, randomizados controlados. Ambos estudios encontraron una asociación positiva significativa de la duración de la alimentación con LM y el neurodesarrollo medido con escala Bayley –uno a los 12 meses de edad corregida y el otro a los 30 meses de edad corregida (16, 17). Nótese que la regulación emocional a los 30 meses también estuvo significativamente asociada con la ingesta de LM (17). Estos primeros estudios prospectivos demostraron menos ECN, sepsis tardía, estadía hospitalaria, y mejores scores en neurodesarrollo en los infantes alimentados predominantemente con LM con FLH en base a leche de vaca durante la hospitalización neonatal. Los estudios que evaluaron si la LM disminuye ROP han tenido resultados mixtos (18-20). Los resultados de ROP asociados a la dosis de LH se discutirán más tarde en este capítulo.

Resultados con nutrición con LHD en infantes prematuros

Históricamente, en la alimentación con LHD del infante prematuro, la leche era con frecuencia cruda es decir no pasteurizada t raramente fortificada (21). En estudios contemporáneos, LHD es pasteurizada y fortificada. Adicionalmente, en la mayoría de los estudios, los infantes prematuros enrolados reciben LM con randomización para recibir LHD o fórmula PT como suplemento para la LM. El ensayo randomizado, no ciego que comparó LHD fortificada exclusiva versus fórmula de PT exclusiva incluyó un FLH a base de leche de vaca que permitió la comparación de una dieta LHD con fórmula de PT. En este estudio de 53 infantes prematuros, aquellos recibiendo la dieta LHD completa tuvieron significativamente menos días de NP. El estudio no mostró diferencia estadísticamente significativa en ECN, pero significativamente menos infantes alimentados por completo con LHD experimentaron ECN quirúrgica (22).

Tabla 1 - Resultados clínicos con fórmula de alimentación en lugar de leche humana donada

Resultado Clínico	Fórmula vs LHD	Fórmula vs LHD Fortificada	Fórmula vs leche de donante como única dieta (no leche materna)	Fórmula vs leche de donante como suplemento de leche materna
Propoción de riesgo (IC 95%)				
Todas las causas sw mortalidad	1.11 (0.81, 1.53)	1.04 (0.17, 1.52)	1.7 (0.71, 4.07)	1.04 (0.74, 1.47)
ECN	1.87 (1.23, 2.85)	1.64 (1.03, 2.61)	4.62 (1.47, 14.56)	1.56 (0.98, 2.47)
Sepsis	0.95 (0.8, 1.14)	0.95 (0.8, 1.14)	1.43 (0.97, 2.11)	0.91 (0.75, 1.10)
Diferencia de media (IC 95%)				
Ganancia ponderal, g/Kg/día	2.51 (1.93, 3.08)	2.37 (1.09, 3.65)	2.65 (1.94, 3.36)	2.22 (1.23, 3.21)
Ganancia en longitud, mm/sem	1.21 (0.77, 1.65)	1.10 (0.33, 1.87)	1.54 (0.98, 2.11)	0.67 (−0.04, 1.38)
Ganancia en perímetro cefálico, mm/sem	0.85 (0.47, 1.23)	0.3 (−0.27, 0.86)	1.36 (0.85, 1.88)	0.24 (−0.32, 0.8)

Reference: Quigley et al.[21]

Una revisión sistemática Cochrane publicada en 2018 incluyó 11 estudios- cuatro comparando fórmula de término con leche sin fortificar, tres comparando fórmula PT con leche sin fortificar y cuatro comparando fórmula PT y leche fortificada en su meta-análisis (21). El RR y los IC 95% para los resultados clínicos en todos los estudios incluidos y específicamente para aquellos comparando fórmula de PT y LHD fortificada se muestran en la Tabla 1. LHD no se asocia a mejoría significativa en todas las causas de mortalidad o infección invasiva comparada con fórmula. Los infantes alimentados con fórmula exhiben un riesgo significativamente más alto de ECN cuando se comparan con infantes prematuros alimentados con LHD e infantes prematuros alimentados con LHD fortificada, pero el riesgo elevado no sigue siendo significativo cuando se compara fórmula de PT y LHD como suplementos de la LM. Meta-análisis previos de fórmula de PT versus LHD no fortificada han generado preocupación acerca de los resultados en neurodesarrollo eran significativamente peores para los infantes alimentados con LHD. Sin embargo, un ensayo doble ciego, randomizado de leche materna suplementada con fórmula de PT o LHD fortificada no mostró diferencia significativa en Bayley-III a los 18 meses de edad corregida (23). Nótese que, LHD producida por nuevos métodos tales como procesamiento de retorta, irradiación ultravioleta, alta presión, y pasteurización a alta temperatura, no tiene ningún estudio publicado acerca de los resultados de salud de los infantes prematuros. Con las conocidas diferencias en cómo el procesamiento afecta los componentes inmunes de la LH, estos productos de LHD requieren estudio antes de que pueda asumirse que también disminuyen el riesgo de ECN (24, 25).

Las comparaciones directas de LHD y LM son limitadas pero en general la LM parece tener efecto más significativo en reducir ECN (26). En una comparación publicada en 2005 de LM fortificada, LHD fortificada, y fórmula PT, los resultados no fueron diferentes entre LHD y fórmula PT como suplementos de la LM, pero los infantes prematuros alimentados sólo con LM tuvieron significativamente menos sepsis tardía aislada y sepsis tardía con ECN como resultado combinado cuando se comparó con los otros dos grupos (27). Adicionalmente, la

dosis de LM parece estar asociada con mejores scores de neurodesarrollo mientras que LHD no lo está (16, 17, 21).

Resultados con dieta de LH exclusiva para infantes PT: (5)

Antes de revisar la evidencia con respecto a dietas exclusivas con LH para infantes pretérmino, debe ser descripta la definición de este término. Antes de la llegada de FLH-basados en leche de vaca y en áreas donde los FLH- basados en LH no están disponibles, dieta exclusiva con LH comúnmente se refiere a dieta de LM y LHD con o sin fortificación con un FLH en base a leche de vaca. Se han observado beneficios con ingesta de LH aún cuando esté suplementada con FLH-en base a leche de vaca. Como se mencionó previamente, muchos de los primeros estudios prospectivos en los EE.UU. que demostraron disminución de ECN con ingesta de LM tenían fortificación con FLH- en base a leche de vaca de las raciones hasta 100ml/kg/d (13-15). En Alemania, se observaron resultados similares comparando infantes amamantados en forma exclusiva (LM y LHD fortificada con FLH basado en leche de vaca). En una cohorte multicéntrica de 1433 infantes de MBPN, los infantes exclusivamente alimentados con leche materna demostraron menos ECN, ROP, y DBP que sus controles alimentados exclusivamente con fórmula (28).

Sin embargo, muchos centros neonatales en todo el mundo mantienen la preocupación acerca de que la exposición a FLH en base a leche de vaca aumenta el riesgo del infante prematuro y, por lo tanto, dan LM o LHD sin ninguna fortificación o fortificando con productos que no contengan proteína de vaca (ej., aceite, minerales, carbohidratos) (29). El potencial déficit nutricional para el infante prematuro que pueda causar esta práctica de no fortificar, requiere mayor estudio. Una revisión Cochrane sistemática demostró mejor ganancia de peso, talla, y CC con fortificación comparada con no fortificación pero no mostró diferencia en la mineralización ósea o el neurodesarrollo (30).

El desarrollo de FLH basados en LH expandió la definición de una dieta exclusiva o solamente de LH. El FLH-en base a LH actualmente disponible es LH pasteurizada concentrada para proveer 1.4 Kcal/mL y 0.06 g/mL de proteína comparado con el estimado de 0.68 Kcal/mL y 0.01 g/mL en la LH no concentrada. Los productos están disponibles para proveer un resultado de 24-30 Kcal/oz para las raciones de LH fortificada. Otros nutrientes como calcio y fósforo son suplementados para proveer fortificación adecuada al infante prematuro. Es de notar que, el volumen de fortificador oscila entre 20 a 50 ml de FLH en 100 mL del volumen total de la ración ingerida (20-50%) y este desplazamiento de la LM debería ser considerado a la luz de los estudios que muestran la importancia de la dosis de LM para el infante prematuro.

En el meta-análisis de 2018 de Jacqueline Miller et al acerca de alimentación con LH en PT MBPN, los estudios categorizados como "LH exclusiva versus FPT exclusiva" incluyen un ensayo randomizado con FLH en base a LH en el grupo de LH exclusiva y 5 ensayos no-randomizados o estudios observacionales incluyendo uno con FLH en base a LH, tres con FLH en base a leche de vaca, y uno que no menciona fortificación (18, 20, 22, 28, 31-33). LH exclusiva comparada con fórmula PT exclusiva estuvo asociada a significativamente menos ECN, pero no hubo significativamente menos sepsis tardía, DBP, o ROP- excepto ROP severa (33).

Dos de seis estudios que definieron "LH exclusiva" para este meta-análisis a los infantes que recibieron LM, LHD, y FLH en base a LH, fueron un ensayo randomizado controlado y una revisión retrospectiva de un solo centro (22, 31, 33). Los otros estudios de FLH a partir de LH incluyen la primera investigación sobre FLH en base a LH (34). En este estudio, todos los infantes podían recibir LM pero eran randomizados para recibir FLH- en base a LH y LHD según necesidad o para recibir FLH en base a leche de vaca y fórmula de PT según necesidad. Los dos grupos demostraron ninguna diferencia en los días de NP que era un marcador surrogante de intolerancia alimentaria y el resultado primario del estudio. Sin embargo, el grupo FLH-base LH/LHD exhibió una incidencia significativamente menor de ECN (34). El cuarto estudio sobre FLH-base LH, incluido en la revisión de 2018 de Miller, es una cohorte retrospectiva multicéntrica de 1528 infantes nacidos <1250 gramos que está incluida en la comparación del meta-análisis de dosis más alta versus más baja de ingesta de LH (35).

El único ensayo ciego, randomizado controlado de FLH- base LH fue publicado en 2018 y, consiguientemente, no está en el meta-análisis de Miller del 2018. Es el único estudio de FLH- base LH donde los infantes no recibieron fórmula PT (36). Ambos grupos de comparación recibieron LM suplementada según necesidad con LHD. Por lo tanto, la única diferencia entre ambos grupos de comparación es la exposición a FLH- base leche de vaca o FLH-base LH. En este estudio de 127 infantes nacidos <1250 gramos, los grupos de comparación no presentaron diferencia significativa en intolerancia alimentaria (resultado primario), ECN, sepsis tardía, DBP, injuria cerebral severa, o mortalidad. La única diferencia entre grupos fue una menor incidencia de ROP severa para los infantes que recibieron FLH-base LH (36). Este hallazgo es de interés y garantiza mayor estudio dado que los marcadores del stress oxidativo están aumentados al adicionar el fortificador en base a leche de vaca en un pequeño estudio observacional (37).

Entonces, los estudios de LH exclusiva muestran que una base de LH (LM y LHD) con un FLH-base leche de vaca está asociado con significativamente menos ECN que con fórmula PT. Potencialmente, evitar la exposición completa a leche de vaca, sea proveyendo raciones sin fortificar o FLH-base LH, está asociada con menos intolerancia o ECN, pero estas

presunciones aún no están apoyadas por un ensayo doble ciego, randomizado, controlado de fortificador base LH versus base leche de vaca o una revisión Cochrane sistemática comparando alimentación con LH fortificada y sin fortificar para los infantes prematuros (30, 36).

Resultados de alimentar con LH (LM o LHD) para infantes prematuros

El meta-análisis de Miller también presenta una comparación de estudios observacionales de alimentar con cualquier LH (LM o LHD) versus fórmula de PT exclusiva, trabajos randomizados de mayor versus menor dosis de LH, y estudios observacionales de mayor versus menor dosis de LH (33). Para ECN, así como LH exclusiva comparada con fórmula de PT exclusiva está asociada con significativamente menor riesgo de enfermedad, también cualquier LH comparada con fórmula PT exclusiva. Adicionalmente, el meta-análisis de los estudios observacionales comparando dosis de LH demuestran significativamente menos ECN, sepsis tardía, DBP, y ROP con dosis más altas de LH (33). Estos estudios observacionales de la dosis de LH son de menor nivel de evidencia que los ensayos randomizados y pueden contener sesgos importantes. Por otra parte, estos estudios representan a más de 4000 infantes lo cual puede proveer poder adecuado para que significativas diferencias sean evidentes (33). Por ahora, el rol de la LH en la protección para ECN es bastante evidente. Su rol en la protección contra sepsis tardía, DBP, y ROP no es tan claro pero puede tener beneficio adicional. Por lo tanto, con la evidencia actual, el cuidado clínico del infante prematuro debería incluir programas para obtener LM y LHD.

Métodos basados en la evidencia para obtener y proveer alimentación con LM para los infantes prematuros

Dado el beneficio conocido para disminuir ECN y el alto potencial para disminuir otras morbilidades de la prematurez, la LM es una poderosa intervención para mejorar resultados en infantes prematuros. Por lo tanto, debería prestarse mucha atención a los métodos para sostener el aporte de LM. Una lista de métodos basados en la evidencia se ofrece en la Tabla 2 (38-43). La iniciación de la expresión de LM debería comenzar temprano para mantener la lactancia y para tener LM disponible, tan pronto como sea posible después de nacer. Como se mencionó previamente, LM es similar al líquido amniótico y está formulada para continuar con el desarrollo de órganos y conferir protección inmune postnatalmente. Así como un niño de término es alimentado inmediatamente después de nacer, el beneficio de la alimentación inmediata o temprana de los infantes prematuros está siendo estudiado. La terapia oral inmune (TOI) o calostro oral es un método para exponer l mucosa bucal del infante prematuro a la LM. Un meta-análisis reciente concluyó que los días hasta la alimentación enteral completa estaban significativamente disminuidos con una diferencia media de 2.58 días en seis estudios de 335 infantes (44). La exploración del efecto inmune

de TOI ha mostrado significativos aumentos en la sIgA y lactoferrina urinaria del infante prematuro con TOI (45).

La evidencia acerca de la edad postnatal óptima para iniciar la alimentación gástrica es limitada, pero hasta ahora, no se ha identificado un momento que sea demasiado temprano. El meta-análisis de los datos muestra que no hay daño en iniciar la alimentación antes de los cuatro días aún en niños con restricción del crecimiento (46). Un estudio de un solo centro acerca de alimentar infantes EBPN en el primer día postnatal no mostró resultados alterados (47). Con el beneficio de la LM para el sistema inmune y la salud intestinal del infante, la rápida provisión postparto de esta terapia debiera ser considerada.

Tabla 2 - Métodos basados en evidencia que sostienen la suplementacón de leche materna en el prematuro.

Extracción manual	Mantener hasta la sem 40 de edad postconcepcional	• Inicio a las 6 hs • Extracción al menos 5 veces/día
	Para un volumen mayor a las 6 sem mantenido hasta que sea dado de alta hospitalaria	• Inicio en hora 1. • Obtener y mantener volumen de leche de 500 cc/día
Con Bomba características	Mantener hasta el alta	• Extracción simultanea de ambas mamas con bomba doble • Garantizar la comodiad de la extracción láctea
Cuidados método canguro	Mantener hasta las 40 sem, asociado con con alta probabilidad de que se mantenega hasta los 6 m	• Realizar cuidados kanguro ilimitados
Soporte hospitalario	Mantener hasta el alta	• Personal adecuado. • Personal de enfermería experto • Soporte de la lactancia por el personal de enfermería

Otras consideraciones en la alimentación con LH para infantes prematuros

Citomegalovirus (CMV) está presente en la leche extraída hasta en un 96% de las mujeres seropositivas, y la infección sintomática por exposición a esta leche ocurre en un subgrupo de infantes prematuros. La pasteurización es el método principal disponible para evitar la exposición a CMV en LM. Adicionalmente, la pasteurización destruye otros microbianos que contaminan la LM extraída potencialmente aumentando el riesgo para infección del infante. En efecto, agencias de seguridad alimentaria de algunos países han recomendado suministrar sólo leche pasteurizada a los infantes prematuros. En estudios realizados para evaluar cómo los resultados difieren entre infantes alimentados con LM cruda y LM pasteurizada, no se observa diferencia significativa en sepsis tardía o ECN (48-50). Se encontraron frecuencias más bajas de DBP en unidades con política de pasteurización, pero este resultado puede no estar asociado con la ingesta de leche y en cambio puede reflejar las conocidas diferencias entre unidades en frecuencia de DBP (49). Un estudio reportó una diferencia significativa en infección CMV, pero infección fue definida como muestra de orina positiva y no necesariamente asociada con síntomas (50). Al no haber evidencia de diferencia significante con la pasteurización de LM y sabiendo los déficits nutricional e inmune con la pasteurización de la leche (51) no se recomienda la pasteurización rutinaria en la actualidad.

Resultados a largo plazo de las dietas con LH para infantes prematuros

Para la población de bebés de término amamantados, LM está asociada con disminución significativa del riesgo de infección a lo largo del primer año postnatal y de riesgo de enfermedad autoinmune y cáncer (52, 53). Aunque estos resultados no han sido estudiados en la población de infantes prematuros, ellos podrían recibir los mismos o similares beneficios de la LM y/o alimentarse al pecho materno durante el primer año de vida. Por lo tanto, proteger la provisión de LM es importante no sólo para proteger al infante prematuro durante la hospitalización neonatal sino para la salud a lo largo de la vida.

El efecto de alimentar con LH sobre el neurodesarrollo aún está en estudio. Como se mencionó anteriormente, estudios de grandes cohortes demostraron un efecto dosis-dependiente sobre los scores en la escala Bayley. Sin embargo, la publicación de Miller demostró que no había diferencia significativa en el meta-análisis de 28 estudios (33). Quizás las mediciones cerebrales con RNM proveerán mayor información para examinar esta cuestión. Un estudio de 180 infantes nacidos <30 sem EG demostró que mayor sustancia gris nuclear profunda a la edad equivalente al término estaba significativamente asociada en forma positiva con el número de días que el infante recibió >50% de LM. Estos hallazgos también se correlacionaron con mejor cociente de inteligencia, y pruebas de matemáticas, memoria de trabajo, y función motora a los 7 años de edad (54).

El otro resultado importante para infantes prematuros y positivamente asociado con el resultado del neurodesarrollo es el crecimiento durante la hospitalización neonatal (55). En un meta-análisis comparando fórmula y LHD, los infantes alimentados con fórmula tuvieron significativamente mayor ganancia de peso y longitud (Tabla 1). La circunferencia craneana también fue significativamente mayor en los infantes alimentados con fórmula excepto cuando se compararon con LHD fortificada (Tabla 1) (21). Para LM fortificada, la mayoría de los infantes parecen alcanzar las metas establecidas para el crecimiento de infantes prematuros, pero pueden requerir densidad calórica y proteica extra (56-58). Es necesaria mayor evaluación para evaluar los resultados del crecimiento de los infantes prematuros con LM o LHD con fortificación.

Conclusión

Las tres décadas de investigación en lo referente a alimentación del infante prematuro con LH están marcadas por limitaciones en la capacidad de randomizar para LM y la diversidad en la práctica tal como LM cruda o pasteurizada, LHD cruda o pasteurizada, y FLH de base leche de vaca y base LH. Pese a estas limitaciones, en meta-análisis de la literatura, LH está consistentemente asociada con menos ECN en la población de infantes MPT. De hecho, los dos métodos más efectivos para disminuir riesgo de ECN son haber nacido a un EG más madura y aumentar la ingesta de LH.

El efecto de alimentar con LH para otras morbilidades no es tan consistentemente evidente en la literatura, pero, específico para la LH exclusiva, ROP severa parece disminuir con esta intervención. De hecho, la dieta con LH exclusiva con FLH en base a LH puede conferir beneficio adicional sobre la dieta con FLH en base a leche de vaca. Otras morbilidades que han demostrado disminuir con la dosis de LH incluyen sepsis tardía, DBP, y ROP (todos los estadíos). En cuanto al ND, pese a que el beneficio no está consistentemente demostrado en meta-análisis, estudios de grandes cohortes y estudios recientes de RNM de cerebro demuestran gran potencial para mejor desarrollo cerebral con la dosis de LM. Para crecimiento del infante prematuro, las dietas exclusivas de LH históricamente estuvieron asociadas con trayectorias antropométricas más bajas, pero las prácticas de FLH proporcionando mayor cantidad de nutrientes están remediando este aspecto. Con el reconocimiento de la investigación mostrando mejores resultados con la dosis de LH, un concepto clave a considerar en el cuidado clínico del infante prematuro es no sólo dar atención al tipo de alimentación cuando se alimenta sino también enfocarse en alimentar en forma consistente con LH especialmente LM. Los protocolos de cuidado clínico deberían reconocer cada día sin proporcionar LH como un riesgo para ECN, ROP severa y potencialmente sepsis tardía y DBP en la población de infantes MPT.

REFERENCIAS

1. Wagner CL, Taylor SN, Johnson D. Host factors in amniotic fluid and breast milk that contribute to gut maturation. Clin Rev Allergy Immunol. 2008;34(2):191–204.
2. Cregan MD, Fan Y, Appelbee A, et al. Identification of nestinpositive putative mammary stem cells in human breastmilk. Cell Tissue Res. 2007;329(1):129–136.
3. Taylor SN, Basile LA, Ebeling M, Wagner CL. Intestinal permeability in preterm infants by feeding type: mother's milk versus formula. Breastfeed Med. 2009;4(1):11–15.
4. Catassi C, Bonucci A, Coppa GV, Carlucci A, Giorgi PL. Intestinal permeability changes during the first month: effect of natural versus artificial feeding. J Pediatr Gastroenterol Nutr. 1995;21(4):383–386.
5. Hassiotou F, Geddes DT, Hartmann PE. Cells in human milk: state of the science. J Hum Lact. 2013;29(2):171–182.
6. Buescher ES. Anti-inflammatory characteristics of human milk: how, where, why. Adv Exp Med Biol. 2001;501:207–222.
7. Rogier EW, Frantz AL, Bruno ME, et al. Lessons from mother: Long-term impact of antibodies in breast milk on the gut microbiota and intestinal immune system of breastfed offspring. Gut Microbes. 2014;5(5):663–668.
8. Ochoa TJ, Sizonenko SV. Lactoferrin and prematurity: a promising milk protein? Biochem Cell Biol. 2017;95(1):22–30.
9. Hamosh M. Protective function of proteins and lipids in human milk. Biol Neonate. 1998;74(2):163–176.
10. Lewis ED, Richard C, Larsen BM, Field CJ. The Importance of Human Milk for Immunity in Preterm Infants. Clin Perinatol. 2017;44(1):23–47.
11. Martin LJ, Woo JG, Geraghty SR, et al. Adiponectin is present in human milk and is associated with maternal factors. Am J Clin Nutr. 2006;83(5):1106–1111.

12. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet (London, England). 1990;336(8730):1519–1523.
13. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus pretermformula. Pediatrics. 1999;103(6 Pt 1):1150–1157.
14. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. Arch Pediatr Adolesc Med. 2003;157(1):66–71.
15. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol. 2007;27(7):428–433.
16. O'Connor DL, Jacobs J, Hall R, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. J Pediatr Gastroenterol Nutr. 2003;37(4):437–446.
17. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007;120(4):e953–e959.
18. Manzoni P, Stolfi I, Pedicino R, et al. Human milk feeding prevents retinopathy of prematurity (ROP) in preterm VLBW neonates. Early Hum Dev. 2013;89(Suppl 1):S64–S68.
19. Heller CD, O'Shea M, Yao Q, et al. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. Pediatrics. 2007;120(1):1–9.
20. Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R. Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants. J Perinatol. 2001;21(6):356–362.
21. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2018;6:CD002971.
22. Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. J Pediatr. 2013;163(6):1592–1595: e1591.
23. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. JAMA. 2016;316(18):1897–1905.
24. Lima HK, Wagner-Gillespie M, Perrin MT, Fogleman AD. Bacteria and Bioactivity in Holder Pasteurized and Shelf-Stable Human Milk Products. Curr Dev Nutr. 2017;1(8):e001438.
25. Pitino MA, Unger S, Doyen A, et al. High hydrostatic pressure processing better preserves the nutrient and bioactive compound composition of human donor milk. J Nutr. 2019.
26. Montjaux-Regis N, Cristini C, Arnaud C, Glorieux I, Vanpee M, Casper C. Improved growth of preterm infants receiving mother's own raw milk compared with pasteurized donormilk. Acta Paediatr. 2011;100(12):1548–1554: (Oslo, Norway: 1992).
27. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics. 2005;116(2):400–406.
28. Spiegler J, Preuss M, Gebauer C, Bendiks M, Herting E, Gopel W. Does breastmilk influence the development of bronchopulmonary dysplasia? J Pediatr. 2016;169:76–80: e74.
29. Stiles S, de Rooy L. Breastfeeding rates at discharge: don't blame the fortifier! A national survey of practice and comparison with NNAP data. Arch Dis Child Fetal Neonatal Ed. 2018;103(6):F597–F598.
30. Brown JV, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. Cochrane Database Syst Rev. 2016(5):Cd000343
31. Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. J Perinatol. 2016;36(3):216–220.

32. Manea A, Boia M, Iacob D, Dima M, Iacob RE. Benefits of early enteral nutrition in extremely low birth weight infants. Singap Med J. 2016;57(11):616–618.
33. Miller J, Tonkin E, Damarell RA, et al. A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. Nutrients. 2018;10(6).
34. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milkbased products. J Pediatr. 2010;156(4):562–567: e561.
35. Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. Breastfeed Med. 2016;11(2):70–74.
36. O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. Am J Clin Nutr. 2018;108(1):108–116.
37. Friel JK, Diehl-Jones B, Cockell KA, et al. Evidence of oxidative stress in relation to feeding type during early life in premature infants. Pediatr Res. 2011;69(2):160–164.
38. Furman L, Minich N, Hack M. Correlates of lactation in mothers of very low birth weight infants. Pediatrics. 2002;109(4):e57.
39. Hallowell SG, Rogowski JA, Spatz DL, Hanlon AL, Kenny M, Lake ET. Factors associated with infant feeding of human milk at discharge from neonatal intensive care: cross-sectional analysis of nurse survey and infant outcomes data. Int J Nurs Stud. 2016;53:190–203.
40. Fewtrell MS, Kennedy K, Ahluwalia JS, Nicholl R, Lucas A, Burton P. Predictors of expressed breast milk volume in mothers expressing milk for their preterm infant. Arch Dis Child Fetal Neonatal Ed. 2016.
41. Flacking R, Ewald U, Wallin L. Positive effect of kangaroo mother care on long-term breastfeeding in very preterm infants. J Obstet Gynecol Neonatal Nurs. 2011;40(2):190–197.
42. Hake-Brooks SJ, Anderson GC. Kangaroo care and breastfeeding of mother-preterm infant dyads 0-18 months: a randomized, controlled trial. Neonatal Netw. 2008;27(3):151–159.
43. Parker LA, Sullivan S, Krueger C, Mueller M. Association of timing of initiation of breastmilk expression on milk volume and timing of lactogenesis stage II among mothers of very low-birth-weight infants. Breastfeed Med. 2015;10(2):84–91.
44. Nasuf AWA, Ojha S, Dorling J. Oropharyngeal colostrum in preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev. 2018;9:CD011921.
45. Lee J, Kim HS, Jung YH, et al. Oropharyngeal colostrums administration in extremely premature infants: an RCT. Pediatrics. 2015;135(2):e357–e366.
46. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev. 2014 (12):CD001970.
47. Hamilton E, Massey C, Ross J, Taylor S. Early enteral feeding in very low birth weight infants. Early Hum Dev. 2014;90(5): 227–230.
48. Cossey V, Vanhole C, Eerdekens A, Rayyan M, Fieuws S, Schuermans A. Pasteurization of mother's own milk for preterm infants does not reduce the incidence of late-onset sepsis. Neonatology. 2013;103(3):170–176.
49. Dicky O, Ehlinger V, Montjaux N, et al. Policy of feeding very preterm infants with their mother's own fresh expressed milk was associated with a reduced risk of bronchopulmonary dysplasia. Acta Paediatr. 2017;106(5):755–762: (Oslo, Norway: 1992).
50. Stock K, Griesmaier E, Brunner B, Neubauer V, Kiechl-Kohlendorfer U, Trawoger R. Pasteurization of breastmilk decreases the rate of postnatally acquired cytomegalovirus infections, but shows a nonsignificant trend to an increased rate of necrotizing enterocolitis in very preterm infants_a preliminary study. Breastfeed Med. 2015;10(2):113–117.

51. Peila C, Moro GE, Bertino E, et al. The effect of holder pasteurization on nutrients and biologically-active components in donor human milk: a review. Nutrients. 2016;8(8).
52. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827–e841.
53. Ip S, Chung M, Raman G, Trikalinos TA, Lau J. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. Breastfeed Med. 2009;4(Suppl 1):S17–S30.
54. Belfort MB, Anderson PJ, Nowak VA, et al. Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born at less than 30 weeks' gestation. J Pediatr. 2016;177:133–139: e131.
55. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics. 2006;117(4):1253–1261.
56. Kim JH, Chan G, Schanler R, et al. Growth and tolerance of preterm infants fed a new extensively hydrolyzed liquid human milk fortifier. J Pediatr Gastroenterol Nutr. 2015;61(6): 665–671.
57. Hair AB, Hawthorne KM, Chetta KE, Abrams SA. Human milk feeding supports adequate growth in infants </= 1250 grams birth weight. BMC Res Notes. 2013;6:459.
58. Hair AB, Bergner EM, Lee ML, et al. Premature infants 750- 1,250 g birth weight supplemented with a novel human milkderived cream are discharged sooner. Breastfeed Med. 2016;11:133–137.

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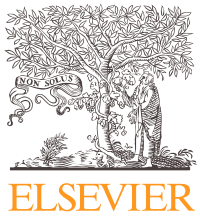

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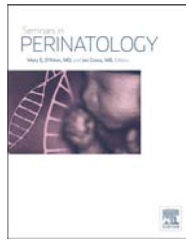

Solely human milk diets for preterm infants

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ARTICLE INFO

Keywords:
Human milk
Preterm infant
Growth
Nutrition

ABSTRACT

Human milk provides not only ideal nutrition for infant development but also immunologic factors to protect from infection and inflammation. For the newborn preterm infant, the natural delivery of milk is not attainable, and instead pumped maternal milk, donor human milk, and human milk fortification are mainstays of clinical care. Current research demonstrates a decreased risk of necrotizing enterocolitis with maternal milk and donor human milk when individually compared to formula and with a complete human milk diet of maternal milk supplemented with donor human milk. The incidence of severe retinopathy of prematurity is decreased with an exclusive human milk diet, and this decrease is more pronounced with human milk-based compared to bovine milk-based human milk fortifier. The incidence of other morbidities such as late-onset sepsis and bronchopulmonary dysplasia is decreased with higher dose of human milk though significant differences are not apparent in exclusive human milk diet studies.

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Introduction

Very preterm birth is associated with increased morbidity and mortality risks. As scientists investigated methods to improve the rate of morbidity-free survival in this population, feeding type, specifically human milk versus infant formula, was discovered as a potential method to enhance very preterm infant outcomes. Yet, study of this effect has been restricted due to innate difficulties in study conduction. Delivery of maternal milk to the infant relies on mother's ability to express milk and, unfortunately, methods to optimize milk expression initiation and continuation, though improving, are not adequate for every mother and, therefore, do not allow randomization to maternal milk. Donor human milk (DHM) diets require removal of microbial contamination, by pasteurization in current human milk outcomes' literature, which decreases both the nutrient and immune-boosting components of human milk. Additionally, nutritional deficits with both maternal milk and especially DHM nutrition respond positively to supplementation with human milk fortifier (HMF). With the association between preterm infant growth and neurodevelopment, this supplementation may be critical to optimizing preterm infant outcomes positively associated with growth trajectory. In addition, a human milk-based HMF is now available in some markets and has revised the definition of a "solely human milk diet" to include maternal milk, DHM, and human milk-based HMF. However, human milk-based HMF availability is not universal, and its high financial cost must be weighed into consideration of its effectiveness. Therefore, bovine milk-based HMF or no fortification remain common practices worldwide. All of these factors complicate investigation of the benefit of the solely human milk diet for preterm infants. Despite this, numerous human milk mechanistic studies, observational studies, clinical trials, and meta-analyses provide evidence as to the best method for preterm infant feeding.

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https://doi.org/10.1053/j.semperi.2019.06.006
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Function of maternal milk

Maternal milk is the ideal nutrition for an infant. Some components may vary by maternal diet, and complementary foods are recommended in the second half of infancy, but, overall, it is the gold standard to which all other feeding types are held. The nutritional needs of a preterm infant vary slightly from those of a full-term infant as certain nutrient delivery is higher to a fetus than to a newborn. When preterm infants miss fetal nutrition, deficits accumulate, and may call for amelioration with nutrient supplementation.

The function of maternal milk goes well beyond nutritional support to the infant as it provides immune support and promotes organ development. Gut development is first supported by amniotic fluid which delivers growth-promoting factors such as epidermal growth factor, growth hormone, transforming growth factor-alpha and beta, erythropoietin, and insulin-like growth factors known to correlate with villus development of the fetus. These same hormones and others, such as glutamine and granulocyte colony stimulating factor, are in human milk and affect maturation and differentiation of the gastrointestinal system through infancy.[1] Additionally, stem cells demonstrating pluripotency have been isolated from human milk and may play a role in epithelial wall development.[2] In clinical studies, maternal milk exposure is associated with decreased intestinal permeability, and, thereby, increased intestinal maturation, for both preterm and term infants.[3,4]

Maternal milk also plays a critical promotion of early immune function. Active leukocytes, predominantly macrophages in colostrum, have been shown in animal studies to transfer through the intestinal epithelium into infant circulation.[5,6] Adaptive immune function is transferred from mother to infant further by secretory IgA (sIgA) which delivers both short-term and long-term protection to the gut through regulation of gut microbiota and intestinal gene expression.[7] Even nutritional elements of maternal milk hold immune function warranting the description 'multifunctional milk components'. For example, lactoferrin chelates free iron and has long been thought to support infant iron absorption and perhaps have an antibacterial effect by decreasing the unbound iron available to bacteria. Yet, this glycoprotein is now known to have a direct stimulation of macrophage phagocytosis and inhibit bacteria, viruses, and fungus through this mechanism and potentially others.[8,9] Another example is the triglyceride product, monoglyceride, which acts as a detergent on pathogen membranes.[9] These multifunctional milk components are critical constituents of the innate immune function delivered by maternal milk. Anti- and pro-inflammatory cytokines, pro-inflammatory cytokine receptor blockers, hormones such as adiponectin, and human milk oligosaccharides are further examples of the expansive and diverse elements delivering immune protection from mother to infant.[1,10,11]

Outcomes with maternal milk diet for preterm infants

In vitro and mechanistic studies of maternal milk show developmental and immunologic function, but how do these processes affect clinical outcome? Unfortunately, the highest level of evidence for clinical study—the blinded, randomized, controlled trial, is not an option since infants cannot be randomized to receive or to not receive maternal milk. Therefore, outcomes are best assessed through prospective cohort studies and meta-analyses of this studies. Lucas and Cole's 1990 *Lancet* publication of a prospective multi-center study of 926 preterm infants demonstrated a decrease in NEC with both maternal milk and pasteurized donor milk compared to formula feeding. They found a sole diet of human milk to be the most effective but benefit was still observed with any human milk intake compared to formula only.[12] This work was followed by three prospective cohort studies focused on early very preterm infant outcomes with maternal milk feeding. Of note, in these three studies, maternal milk was fortified with bovine milk-based HMF at 100 ml/kg/day. In the first study, 108 preterm infants fed at least 50 ml/kg/day maternal milk were compared to exclusively preterm formula-fed infants. Infants fed this proportion of fortified human milk exhibited less NEC, less late-onset sepsis, and a significantly shorter length of hospital stay.[13] In the second study, 119 very low birthweight (VLBW) infants were compared based on receiving no maternal milk or 1–24, 25–49, or ≥50 ml/kg/day for the first postnatal month. Similar to the previous study, they found significantly less sepsis episodes with ≥50 ml/kg/day. They did not find a significant difference in NEC as seen previously.[14] In the third study, instead of measuring ml/kg/day of maternal milk, the comparison was <50% or ≥50% in the first 14 postnatal days. In 202 VLBW infants, the risk of NEC was significantly lower in the infants receiving ≥50% feeds as maternal milk.[15]

Maternal milk is also thought to have not only an effect on gut development but also on brain development. The potential effect of maternal milk intake on preterm infant neurodevelopment was evaluated in the databases of two large, randomized controlled trials. Both studies found a significant positive association of the duration of maternal milk feedings and neurodevelopment as measured by Bayley Scales of Infant and Toddler Development Mental Index—one at 12 months' corrected age and the other up to 30 months' corrected age.[16,17] Of note, emotional regulation at 30 months also was significantly associated with maternal milk intake.[17] These early, prospective studies demonstrated lower NEC, late-onset sepsis, length of stay, and higher neurodevelopmental scores for infants fed predominantly maternal milk-fed with bovine-based fortification during birth hospitalization. Studies evaluating whether maternal milk decreases retinopathy of prematurity (ROP) have had mixed results.[18–20] ROP outcomes associated with human milk dose will be discussed later in this chapter.

Outcomes with donor human milk diet for preterm infants

Historically, in preterm infant DHM feeding, the milk was often raw meaning not pasteurized and rarely fortified.[21] In contemporary studies, DHM is pasteurized and fortified. Additionally, in most studies, the enrolled preterm infants receive maternal milk with randomization to receive either

Table 1 – Clinical outcomes with feeding formula instead of donor human milk.[1]

Clinical outcome	Formula versus DHM trials	Formula versus Fortified DHM trials	Formula versus donor milk as the sole diet (no mother's milk)	Formula versus DHM as a supplement to mother's milk trials
Risk ratio (95% confidence interval)				
All-cause mortality	1.11 (0.81, 1.53)	1.04 (0.17, 1.52)	1.7 (0.71, 4.07)	1.04 (0.74, 1.47)
NEC	1.87 (1.23, 2.85)	1.64 (1.03, 2.61)	4.62 (1.47, 14.56)	1.56 (0.98, 2.47)
Invasive infection	0.95 (0.8, 1.14)	0.95 (0.8, 1.14)	1.43 (0.97, 2.11)	0.91 (0.75, 1.10)
Mean Difference (95% confidence interval)				
Weight gain, g/kg/day	2.51 (1.93, 3.08)	2.37 (1.09, 3.65)	2.65 (1.94, 3.36)	2.22 (1.23, 3.21)
Length gain, mm/week	1.21 (0.77, 1.65)	1.10 (0.33, 1.87)	1.54 (0.98, 2.11)	0.67 (−0.04, 1.38)
Head circumference gain, mm/week	0.85 (0.47, 1.23)	0.3 (−0.27, 0.86)	1.36 (0.85, 1.88)	0.24 (−0.32, 0.8)

Reference: Quigley et al.[21]

DHM or preterm formula as a supplement to maternal milk. The one non-blinded randomized trial to compare exclusive fortified DHM versus exclusive preterm formula included a human milk-based HMF which allowed a comparison of a complete DHM diet to preterm formula. In this study of 53 preterm infants, those receiving the complete DHM diet had significantly less days of parenteral nutrition. The study showed no statistically significant difference in NEC incidence, but significantly less infants fed the complete DHM diet experienced surgical NEC.[22]

A Cochrane Library systematic review published in 2018 included 11 studies—four comparing term formula with unfortified milk, three comparing preterm formula with unfortified milk and four comparing preterm formula and fortified milk in its meta-analysis.[21] The risk ratio and 95% confidence intervals for clinical outcomes in all included studies and specifically for those comparing preterm formula and fortified DHM are shown in Table 1. DHM is not associated with significant improvement in all-cause mortality or invasive infection compared to formula. Formula-fed infants exhibit a significantly higher risk of NEC when compared with DHM-fed preterm infants and fortified DHM-fed preterm infants, but the higher risk is no longer significant when comparing preterm formula and DHM as supplements to maternal milk. Previous meta-analyses of preterm formula versus unfortified donor human milk have raised concern that neurodevelopmental outcomes were significantly worse for the donor milk fed infants. However, a double-blind, randomized trial of maternal milk supplemented with either preterm formula or fortified DHM showed no significant difference in Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at 18 months' correct age.[23] Of note, DHM produced by newer methods such as retort processing, ultraviolet irradiation, high-pressure, and high-heat pasteurization have no published study regarding preterm infant health outcomes. With known differences in how processing effects human milk immune components, these DHM products require study before they can be assumed to also decrease NEC risk.[24,25]

Direct comparisons of DHM and maternal milk are limited but overall maternal milk appears to have a more significant effect in reducing necrotizing enterocolitis.[26] In a 2005 published comparison of fortified maternal milk, fortified donor milk, and preterm formula, outcomes were no different between DHM and preterm formula as supplements to maternal milk feeds, but preterm infants fed only fortified maternal milk had significantly less late-onset sepsis alone and late-onset sepsis and NEC as a combined outcome when compared to the other two groups.[27] Additionally, maternal milk dose appears to be associated with improved neurodevelopmental scores while DHM does not.[16,17,21]

Outcomes with exclusive human milk diet for preterm infants: (5)

Before reviewing the evidence regarding exclusive human milk diets for preterm infants, the definition of this term must be described. Prior to the advent of a human milk-based HMF and in areas where human milk-based HMF remains unavailable, exclusive human milk diet commonly refers to a diet of maternal milk and DHM with one or both fortified with a bovine milk-based HMF. Benefits are observed with human milk intake even when bovine milk-based HMF is supplemented. As mentioned previously, many of the first United States-based prospective studies demonstrating decreased NEC with intake of maternal milk had bovine milk-based fortification of feeds at 100 ml/kg/day.[13–15] In Germany, similar results have been observed comparing exclusively breastmilk-fed (bovine milk-based fortified maternal milk and DHM) with formula-fed infants. In a multicenter cohort of 1433 VLBW infants, the exclusively breastmilk-fed infants demonstrated less NEC, ROP, and bronchopulmonary dysplasia (BPD) than their exclusively formula-fed counterparts.[28]

However, many neonatal care centers worldwide remain concerned that exposure to bovine milk-based HMF increases the preterm infant's risk of NEC and, therefore, give maternal milk or DHM without any fortification or with fortification with products not containing bovine protein (e.g. oil, minerals, carbohydrate).[29] The potential of this unfortified feeding practice to cause preterm infant nutrient deficit requires further study. A Cochrane Library systematic review demonstrated improved weight, length, and head circumference gain with fortification compared to no fortification but showed no difference in bone mineralization or neurodevelopment.[30]

The development of human milk-based HMF expanded the definition of an exclusive or solely human milk diet. The currently available human milk-based HMF is pasteurized

human milk that is concentrated to provide 1.4 kcal/mL and 0.06 g/mL protein compared to the estimated 0.68 kcal/mL and 0.01 g/mL in unconcentrated human milk. Products are available to provide a result of 24–30 kcal/oz for fortified human milk feeds. Other nutrients such as calcium and phosphorus are supplemented to provide adequate fortification to the preterm infant. Of note, the volume of fortifier ranges from 20 to 50 ml HMF in 100 mL total feed volume (20–50%) and this displacement of maternal milk should be considered in light of studies showing the importance of maternal milk dose to the preterm infant.

In the 2018 meta-analysis of human milk feeding in VLBW infants by Jacqueline Miller et al, the studies categorized as "exclusive human milk versus exclusive preterm formula" include one randomized trial with human milk-based HMF in the exclusive human milk group and five non-randomized trials or observation studies including one with human milk-based HMF, three with bovine milk-based HMF, and one with no mention of fortification.[18,20,22,28,31–33] Exclusive human milk compared to exclusive preterm formula was associated with significantly less necrotizing enterocolitis, but not late onset sepsis, BPD, or ROP except severe ROP was significantly reduced with an exclusive human milk diet.[33]

Two of the six studies defined as "exclusive human milk" for this meta-analysis defined "exclusive human milk" as infants receiving maternal milk, DHM, and human milk-based HMF were a randomized, controlled trial described previously and a single-center retrospective review.[22,31,33] The other studies of human milk-based HMF include the first investigation of the human milk-based HMF.[34] In this study, all infants could receive maternal milk but otherwise were randomized to receive human milk-based HMF and donor human milk as needed or to receive bovine milk-based HMF and preterm formula as needed. The two groups demonstrated no difference in days of parenteral nutrition which was a surrogate marker for feeding intolerance and the study's primary outcome. However, the human milk-based HMF/DHM group exhibited a significantly lower incidence of NEC.[34] The fourth human milk-based HMF study, included in the 2018 Miller et al review, is a multi-center retrospective cohort of 1528 infants born <1250 grams that is included in the meta-analysis' comparison of higher versus lower dose of human milk intake.[35]

The only blinded, randomized controlled trial of human milk-based HMF was published in 2018 and, consequently, is not in the Miller et al meta-analysis. It is the only study of human milk-based HMF where no infants received preterm formula.[36] Both comparison groups received maternal milk supplemented as needed with DHM. Therefore, the only difference between the comparison groups is exposure to bovine milk-based HMF or human milk-based HMF. In this study of 127 infants born <1250 grams, the comparison groups had no significant different in feeding intolerance (the primary outcome), necrotizing enterocolitis, late onset sepsis, BPD, severe brain injury, or mortality. The only difference between groups was a lower incidence of severe ROP for the infants receiving the human milk-based HMF.[36] This finding is of interest and warrants further study since markers of oxidative stress are increased with the addition of bovine milk-based fortifier in a small observational study.[37]

Hence, the studies of exclusive human milk diet demonstrate that a human milk-base (maternal milk and DHM) with bovine milk-based fortifier is associated with significantly less NEC than preterm formula. Potentially, avoiding all bovine milk exposure, either by feeding unfortified feeds or provider human milk-based fortifier, is associated with less feeding intolerance or NEC, but these assumptions are not supported by a double-blinded randomized, controlled trial of human versus bovine-milk based fortifier or a Cochrane Library systematic review comparing fortified and unfortified human milk feeds for preterm infants.[30,36]

Outcomes with any human milk (maternal milk or DHM) diet for preterm infants

The Miller et al meta-analysis also presents a comparison of observational studies of any human milk versus exclusive preterm formula, randomized trials of higher versus lower dose human milk, and observational studies of higher versus lower dose human milk.[33] For NEC, just as exclusive human milk compared to exclusive preterm formula is associated with significantly less disease risk, so is any human milk compared to exclusive preterm formula. Additionally, meta-analysis of observational studies comparing dose of human milk demonstrate significantly less NEC, late onset sepsis, BPD, and ROP with higher human milk dose.[33] These observational studies of human milk dose are a lower level of evidence than randomized trials and may contain significant bias. On the other hand, these studies represent over 4000 infants which may provide adequate power for significant differences to be evident.[33] For now, the role of human milk in protection from NEC is quite evident. Its role in protection from late onset sepsis, BPD, and ROP is not quite as clear but may be additional benefit. Therefore, with current evidence, preterm infant clinical care should include programs to obtain maternal milk and DHM.

Evidence-based methods to obtain and provide maternal milk diet for preterm infants

With the known benefit to decrease NEC and the high potential to decrease other preterm infant morbidities, maternal milk is a powerful intervention to improve preterm infant outcomes. Therefore, great attention should be given to methods to sustain maternal milk supply. A list of evidence-based methods is provided in Table 2.[38–43] Initiation of maternal milk expression should start early to sustain maternal milk and to have maternal milk available as soon as possible after birth. As mentioned previously, maternal milk is similar to amniotic fluid and is formulated to continue organ development and confer immune protection postnatally. Just as a full-term infant is fed immediately after birth, the benefit of immediate or early feeding of preterm infants is being elucidated. Oral immune therapy (OIT) or oral colostrum care is a method to expose the preterm infant buccal mucosa to maternal milk. A recent meta-analysis concluded that days to full enteral feeds were significantly reduced with mean difference of 2.58 days in six studies of 335 infants.[44] Exploration

Table 2 – Evidenced-based methods to sustain maternal milk supply for preterm infants.

Milk expression	To sustain until 40 weeks post-menstrual age	• Initiation by 6 h[38] • Expressing at least 5 times/day[38]
	For a higher volume at 6 postnatal weeks	• Initiation by 1 h[43]
	To sustain until infant's hospital discharge	• Obtain and maintain 500 ml/day milk volume[40]
Breast pump characteristics	To sustain until infant's hospital discharge	• Pump both breast simultaneously with a double pump[40] • Ensure breast pump comfort[40]
Kangaroo care	To sustain until 40 weeks PMA and associated with great likelihood of sustaining until 6 months	• Perform unlimited kangaroo care[41,42]
Hospital support	To sustain until infant's hospital discharge	• Adequate staffing[39] • Knowledgeable nursing staff[39] • Nursing staff supportive of breast feeding[39]

of the immune effect of OIT has shown significant increases in preterm infant urinary sIgA and lactoferrin with OIT.[45]

Evidence regarding the appropriate postnatal age at which to initiate gastric feedings is limited, but, as of yet, no time has been identified as being too early. Meta-analysis of the data shows no harm in initiating feeds at less than four days even in growth-restricted infants.[46] A single-center study of feeding extremely low birth weight infants in the first postnatal showed no detrimental outcomes.[47] With the benefit of maternal milk to the infant immune system and gut health, rapid post-birth provision of this therapy should be considered.

Other considerations in human milk diets for preterm infants

Cytomegalovirus (CMV) is present in milk expressed by up to 96% of seropositive women, and symptomatic infection from exposure to this milk occurs in a subset of preterm infants. Pasteurization is the predominant method available to avoid exposure to CMV in maternal milk. Additionally, pasteurization destroys other microbials contaminating expressed maternal milk that potentially may increase the infant's risk for infection. In fact, some countries' food safety agencies have recommended only feeding pasteurized milk to preterm infants. In studies performed to evaluate how outcomes differ between infants fed raw maternal milk and pasteurized maternal milk, no significant difference is observed in late onset sepsis or NEC.[48–50] Lower BPD rates were found in units without pasteurization policies, but this result may not be associated with milk intake and instead may reflect known unit differences in BPD rates.[49] One study did report a significant difference in CMV infection, but infection was defined as a positive urine sample and not necessarily associated with symptoms.[50] With no significant benefit evident with pasteurization of maternal milk and with the knowledge of immune and nutritional deficits with milk pasteurization[51], routine pasteurization of maternal milk is not recommended at this time.

Long-term outcomes of human milk diets for preterm infants

For the full-term breastfeeding population, maternal milk is associated with significant decrease in infection risk through the first postnatal year and with long-term autoimmune and cancer risks.[52,53] Even though these outcomes have not been studied in the preterm infant population, they likely receive the same or similar benefits to maternal milk and/or breastfeeding through the first postnatal year. Therefore, protecting maternal milk supply is important not only to protect the preterm infant during birth hospitalization but for life-long health.

The effect of the human milk diet on neurodevelopment is still being elucidated. As mention previously, large cohort studies demonstrated a dose-dependent effect on Bayley Scales of Infant and Toddler Development scores. However, the Miller et al publication demonstrated no significant difference in meta-analysis of 28 studies.[33] Perhaps MRI brain measurements will provide further information to address this question. A study of 180 infants born <30 weeks' PMA demonstrated greater deep nuclear gray matter at term equivalent age was significantly positively associated with the number of days on which infants received >50% breast milk. These findings also correlated with better intelligence quotient, mathematics, working memory, and motor function tests at 7 years of age.[54]

The other outcome important for preterm infants and positively associated with neurodevelopmental outcome is growth during the birth hospitalization.[55] In a meta-analysis comparing formula and DHM, the formula-fed infants have significantly higher weight and length gain (Table 1). Head circumference also was significantly higher in the formula-fed infants except for when compared to fortified DHM (Table 1).[21] For fortified maternal milk, the majority of infants appear to reach the goals set for preterm infant growth, but may require extra caloric and protein density.[56–58] Further research is needed to evaluate the growth outcomes of preterm infants on both maternal and donor human milk with fortification.

Conclusion

The three decades of research regarding human milk feeding of the preterm infant have been marked by limitations in the ability to randomize to maternal milk and diversity in practice such as raw or pasteurized maternal milk, raw or pasteurized DHM, and bovine milk-based and human milk-based HMF. Despite these limitations, in meta-analysis of the literature, human milk is associated consistently with less NEC in the very preterm infant population. In fact, the two most effective methods to decrease NEC risk are to be born at a more mature gestational age and to increase human milk intake.

The human milk diet's effect on other morbidities is not as consistently evident in the literature, but, specific to the solely human milk diet, severe retinopathy of prematurity appears decreased with this feeding intervention. In fact, the exclusive human milk diet with human milk-based HMF may confer added benefit over a diet with bovine milk-based HMF. Other morbidities shown to decrease with dose of human milk include late-onset sepsis, BPD, and ROP (all stages). Regarding neurodevelopment, though benefit is not consistently demonstrated in meta-analysis, large cohort studies and recent brain MRI studies demonstrate great potential for improved brain development with maternal milk dose. For preterm infant growth, exclusive human milk diets historically were associated with lower anthropometric trajectories, but HMF practices delivering higher nutrient content are remedying this issue. With recognition of the research supporting improved outcomes with human milk dose, a key concept to consider in preterm infant clinical care is to not only give attention to the feeding type when feeding but also to focus on consistent feeding of human milk especially maternal milk. Clinical care protocols should recognize every day without human milk delivery as a risk for necrotizing enterocolitis, severe ROP and potentially late-onset sepsis and bronchopulmonary dysplasia in the very preterm infant population.

Disclosure

The author reports no proprietary or commercial interest in any product mentioned or concept discussed in this article.

REFERENCES

1. Wagner CL, Taylor SN, Johnson D. Host factors in amniotic fluid and breast milk that contribute to gut maturation. *Clin Rev Allergy Immunol*. 2008;34(2):191–204.
2. Cregan MD, Fan Y, Appelbee A, et al. Identification of nestin-positive putative mammary stem cells in human breastmilk. *Cell Tissue Res*. 2007;329(1):129–136.
3. Taylor SN, Basile LA, Ebeling M, Wagner CL. Intestinal permeability in preterm infants by feeding type: mother's milk versus formula. *Breastfeed Med*. 2009;4(1):11–15.
4. Catassi C, Bonucci A, Coppa GV, Carlucci A, Giorgi PL. Intestinal permeability changes during the first month: effect of natural versus artificial feeding. *J Pediatr Gastroenterol Nutr*. 1995;21(4):383–386.
5. Hassiotou F, Geddes DT, Hartmann PE. Cells in human milk: state of the science. *J Hum Lact*. 2013;29(2):171–182.
6. Buescher ES. Anti-inflammatory characteristics of human milk: how, where, why. *Adv Exp Med Biol*. 2001;501:207–222.
7. Rogier EW, Frantz AL, Bruno ME, et al. Lessons from mother: Long-term impact of antibodies in breast milk on the gut microbiota and intestinal immune system of breastfed offspring. *Gut Microbes*. 2014;5(5):663–668.
8. Ochoa TJ, Sizonenko SV. Lactoferrin and prematurity: a promising milk protein? *Biochem Cell Biol*. 2017;95(1):22–30.
9. Hamosh M. Protective function of proteins and lipids in human milk. *Biol Neonate*. 1998;74(2):163–176.
10. Lewis ED, Richard C, Larsen BM, Field CJ. The Importance of Human Milk for Immunity in Preterm Infants. *Clin Perinatol*. 2017;44(1):23–47.
11. Martin LJ, Woo JG, Geraghty SR, et al. Adiponectin is present in human milk and is associated with maternal factors. *Am J Clin Nutr*. 2006;83(5):1106–1111.
12. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. *Lancet (London, England)*. 1990;336(8730):1519–1523.
13. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics*. 1999;103(6 Pt 1):1150–1157.
14. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. *Arch Pediatr Adolesc Med*. 2003;157(1):66–71.
15. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *J Perinatol*. 2007;27(7):428–433.
16. O'Connor DL, Jacobs J, Hall R, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. *J Pediatr Gastroenterol Nutr*. 2003;37(4):437–446.
17. Vohr BR, Poindexter BB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics*. 2007;120(4):e953–e959.
18. Manzoni P, Stolfi I, Pedicino R, et al. Human milk feeding prevents retinopathy of prematurity (ROP) in preterm VLBW neonates. *Early Hum Dev*. 2013;89(Suppl 1):S64–S68.
19. Heller CD, O'Shea M, Yao Q, et al. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. *Pediatrics*. 2007;120(1):1–9.
20. Hylander MA, Strobino DM, Pezzullo JC, Dhanireddy R. Association of human milk feedings with a reduction in retinopathy of prematurity among very low birthweight infants. *J Perinatol*. 2001;21(6):356–362.
21. Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database Syst Rev*. 2018;6:CD002971.
22. Cristofalo EA, Schanler RJ, Blanco CL, et al. Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *J Pediatr*. 2013;163(6):1592–1595: e1591.
23. O'Connor DL, Gibbins S, Kiss A, et al. Effect of supplemental donor human milk compared with preterm formula on neurodevelopment of very low-birth-weight infants at 18 months: a randomized clinical trial. *JAMA*. 2016;316(18):1897–1905.
24. Lima HK, Wagner-Gillespie M, Perrin MT, Fogleman AD. Bacteria and Bioactivity in Holder Pasteurized and Shelf-Stable Human Milk Products. *Curr Dev Nutr*. 2017;1(8):e001438.
25. Pitino MA, Unger S, Doyen A, et al. High hydrostatic pressure processing better preserves the nutrient and bioactive compound composition of human donor milk. *J Nutr*. 2019.
26. Montjaux-Regis N, Cristini C, Arnaud C, Glorieux I, Vanpee M, Casper C. Improved growth of preterm infants receiving mother's own raw milk compared with pasteurized donor milk. *Acta Paediatr*. 2011;100(12):1548–1554: (Oslo, Norway: 1992).
27. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*. 2005;116(2):400–406.
28. Spiegler J, Preuss M, Gebauer C, Bendiks M, Herting E, Gopel W. Does breastmilk influence the development of bronchopulmonary dysplasia? *J Pediatr*. 2016;169:76–80: e74.
29. Stiles S, de Rooy L. Breastfeeding rates at discharge: don't blame the fortifier! A national survey of practice and comparison with NNAP data. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(6):F597–F598.
30. Brown JV, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database Syst Rev*. 2016(5):Cd000343.

31. Assad M, Elliott MJ, Abraham JH. Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *J Perinatol*. 2016;36(3):216–220.
32. Manea A, Boia M, Iacob D, Dima M, Iacob RE. Benefits of early enteral nutrition in extremely low birth weight infants. *Singap Med J*. 2016;57(11):616–618.
33. Miller J, Tonkin E, Damarell RA, et al. A systematic review and meta-analysis of human milk feeding and morbidity in very low birth weight infants. *Nutrients*. 2018;10(6).
34. Sullivan S, Schanler RJ, Kim JH, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr*. 2010;156(4):562–567: e561.
35. Hair AB, Peluso AM, Hawthorne KM, et al. Beyond necrotizing enterocolitis prevention: improving outcomes with an exclusive human milk-based diet. *Breastfeed Med*. 2016;11(2):70–74.
36. O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. *Am J Clin Nutr*. 2018;108(1):108–116.
37. Friel JK, Diehl-Jones B, Cockell KA, et al. Evidence of oxidative stress in relation to feeding type during early life in premature infants. *Pediatr Res*. 2011;69(2):160–164.
38. Furman L, Minich N, Hack M. Correlates of lactation in mothers of very low birth weight infants. *Pediatrics*. 2002;109(4):e57.
39. Hallowell SG, Rogowski JA, Spatz DL, Hanlon AL, Kenny M, Lake ET. Factors associated with infant feeding of human milk at discharge from neonatal intensive care: cross-sectional analysis of nurse survey and infant outcomes data. *Int J Nurs Stud*. 2016;53:190–203.
40. Fewtrell MS, Kennedy K, Ahluwalia JS, Nicholl R, Lucas A, Burton P. Predictors of expressed breast milk volume in mothers expressing milk for their preterm infant. *Arch Dis Child Fetal Neonatal Ed*. 2016.
41. Flacking R, Ewald U, Wallin L. Positive effect of kangaroo mother care on long-term breastfeeding in very preterm infants. *J Obstet Gynecol Neonatal Nurs*. 2011;40(2):190–197.
42. Hake-Brooks SJ, Anderson GC. Kangaroo care and breastfeeding of mother-preterm infant dyads 0-18 months: a randomized, controlled trial. *Neonatal Netw*. 2008;27(3):151–159.
43. Parker LA, Sullivan S, Krueger C, Mueller M. Association of timing of initiation of breastmilk expression on milk volume and timing of lactogenesis stage II among mothers of very low-birth-weight infants. *Breastfeed Med*. 2015;10(2):84–91.
44. Nasuf AWA, Ojha S, Dorling J. Oropharyngeal colostrum in preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev*. 2018;9:CD011921.
45. Lee J, Kim HS, Jung YH, et al. Oropharyngeal colostrum administration in extremely premature infants: an RCT. *Pediatrics*. 2015;135(2):e357–e366.
46. Morgan J, Young L, McGuire W. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev*. 2014 (12):CD001970.
47. Hamilton E, Massey C, Ross J, Taylor S. Early enteral feeding in very low birth weight infants. *Early Hum Dev*. 2014;90(5): 227–230.
48. Cossey V, Vanhole C, Eerdekens A, Rayyan M, Fieuws S, Schuermans A. Pasteurization of mother's own milk for preterm infants does not reduce the incidence of late-onset sepsis. *Neonatology*. 2013;103(3):170–176.
49. Dicky O, Ehlinger V, Montjaux N, et al. Policy of feeding very preterm infants with their mother's own fresh expressed milk was associated with a reduced risk of bronchopulmonary dysplasia. *Acta Paediatr*. 2017;106(5):755–762: (Oslo, Norway: 1992).
50. Stock K, Griesmaier E, Brunner B, Neubauer V, Kiechl-Kohlendorfer U, Trawoger R. Pasteurization of breastmilk decreases the rate of postnatally acquired cytomegalovirus infections, but shows a nonsignificant trend to an increased rate of necrotizing enterocolitis in very preterm infants–a preliminary study. *Breastfeed Med*. 2015;10(2):113–117.
51. Peila C, Moro GE, Bertino E, et al. The effect of holder pasteurization on nutrients and biologically-active components in donor human milk: a review. *Nutrients*. 2016;8(8).
52. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3):e827–e841.
53. Ip S, Chung M, Raman G, Trikalinos TA, Lau J. A summary of the Agency for Healthcare Research and Quality's evidence report on breastfeeding in developed countries. *Breastfeed Med*. 2009;4(Suppl 1):S17–S30.
54. Belfort MB, Anderson PJ, Nowak VA, et al. Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born at less than 30 weeks' gestation. *J Pediatr*. 2016;177:133–139: e131.
55. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics*. 2006;117(4):1253–1261.
56. Kim JH, Chan G, Schanler R, et al. Growth and tolerance of preterm infants fed a new extensively hydrolyzed liquid human milk fortifier. *J Pediatr Gastroenterol Nutr*. 2015;61(6): 665–671.
57. Hair AB, Hawthorne KM, Chetta KE, Abrams SA. Human milk feeding supports adequate growth in infants </= 1250 grams birth weight. *BMC Res Notes*. 2013;6:459.
58. Hair AB, Bergner EM, Lee ML, et al. Premature infants 750-1,250 g birth weight supplemented with a novel human milk-derived cream are discharged sooner. *Breastfeed Med*. 2016;11:133–137.