La Placenta y el Neurodesarrollo en Recién Nacidos Prematuros

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Brechas en Educación

1. Los clínicos debieran reconocer que los neonatos prematuros están en riesgo de déficit del neurodesarrollo secundario a injuria y alteración madurativa del cerebro.
2. Los proveedores neonatales deberían comprender las implicancias de la insuficiencia placentaria y corioamnionitis en el neurodesarrollo de los neonatos prematuros.

Resumen

En el cuidado de niños prematuros, un desafío mayor se basa en la comprensión de los contribuyentes a la dismaduración e injuria del cerebro, los cuales sirven como precursores del déficit del neurodesarrollo en la infancia. Además de las varias exposiciones adversas que el RN prematuro encuentra en la vida postnatal, los antecedentes de la placenta del parto prematuro antes y después, pueden afectar la dismaduración e injuria del cerebro. La placenta anormal es una frecuente complicación del embarazo, y las patologías placentarias, tales como la insuficiencia placentaria y la corioamnionitis aguda, con frecuencia preceden al parto prematuro.

La insuficiencia placentaria es la causa principal de la restricción del crecimiento fetal y actúa vía la hipoxia crónica fetal. Durante la hipoxia fetal, la redistribución del gasto cardíaco al cerebro representa una importante respuesta adaptativa fetal; sin embargo, la protección vascular del cerebro no asegura el crecimiento cerebral normal. La restricción del crecimiento fetal temprano, que está asociada con una placenta hipermadura y mal perfundida, resulta en déficit del neurodesarrollo independiente de la duración de la gestación en recién nacidos prematuros. La corioamnionitis aguda está caracterizada por la infiltración de la placenta por células inmunes y con frecuencia resulta de infección que induce respuesta inflamatoria. La corioamnionitis puede llevar a síndrome de respuesta fetal inflamatoria y parto pretérmino, y entonces puede agregar a la injuria cerebral neonatal subsiguiente. La salud placentaria debería ser examinada para la comprensión de los orígenes de la dismadurez e injuria del cerebro prematuro, y el subsiguiente déficit del neurodesarrollo.

Objetivos Luego de la lectura, los lectores deberían poder:

1- Describir las características de la dismadurez e injuria del cerebro pretérmino
2- Discutir la fisiopatología de la protección cerebral en la insuficiencia placentaria.
3- Describir la fisiopatología del síndrome de respuesta inflamatoria fetal en la corioamnionitis

INTRODUCCIÓN

Pese a que las tasas de sobrevida de los neonatos muy PT han aumentado en décadas recientes, reflejando avances crecientes en el cuidado intensivo neonatal, el nacimiento prematuro continúa siendo una causa mayor de discapacidad en la infancia y durante la vida (1). La OMS estima que aproximadamente 15 millones de infantes prematuros (1 cada 10 nacidos vivos) nacen con menos de 37 semanas de gestación en todo el mundo cada año. Entre los sobrevivientes de nacimiento MPT, que es definido como nacer con ≤ 32 semanas de gestación, aproximadamente 5% a 10% tienen déficits motores mayores tales como PC pero una proporción mucho mayor tiene alteraciones cognitivas, conductuales, o sensoriales que se manifiestan más tarde en la niñez (2, 3). Estos déficits relativamente leves resultan en dificultades académicas y persisten hasta la adultez (4, 5). La carga económica y social del nacimiento prematuro es, por lo tanto, considerable.

En la última década, la vulnerabilidad del cerebro prematuro está siendo crecientemente reconocida como un problema de *dismaduración* más que exclusivamente por injurias necróticas (6). Muchos grupos han mostrado que aspectos del curso postnatal del neonato pretérmino- incluyendo la ventilación mecánica, infecciones, malnutrición, y procedimientos dolorosos- contribuyen a la dismaduración del cerebro (7, 8, 9). Sin embargo, dado que el nacimiento prematuro es un síndrome con frecuencia atribuible a patologías placentarias, la dismaduración del cerebro que lleva a posteriores déficits en el neurodesarrollo puede tener sus orígenes en la perturbación de la fisiología del útero. Hay importante evidencia de que el cerebro del feto que nacerá prematuro está funcionalmente alterado en relación al del feto que subsiguientemente nacerá a término (10). En un estudio primero en su clase de 36 mujeres gestantes, Thomason et al mostraron que la conectividad del cerebro estuvo disminuida en fetos que subsiguientemente nacieron prematuros, sugiriendo que el déficit del neurodesarrollo después del parto prematuro puede tener orígenes intraútero (10). En otras palabras, el cerebro del feto destinado a ser nacido prematuro puede desviarse de su trayectoria normal de desarrollo, presumiblemente relacionado, al menos en parte, al ambiente in utero que llevará eventualmente al nacimiento prematuro.

La placenta es el tejido clave regulando el ambiente fetal, mediando el intercambio de nutrientes y productos de desecho entre las circulaciones materna y fetal. Las alteraciones de la placenta se encuentran en muchas condiciones antenatales que llevan al nacimiento prematuro y pueden contribuir a pobre neurodesarrollo (Figura). Estas alteraciones pueden ser clasificadas en forma amplia como placenta malperfundida y placenta inflamada. La placenta malperfundida, como en la insuficiencia placentaria, es un precursor común de la restricción del crecimiento fetal (RCF) y preeclampsia, los cuales pueden preceder y complicar el parto prematuro (11).

La placenta inflamada, como en la corioamnionitis aguda, es un gatillo para el parto prematuro, y puede llevar al síndrome de respuesta inflamatoria fetal (FIRS) a través de la liberación de citokinas proinflamatorias (12).

Una mejor comprensión de la relación entre la placenta y el neurodesarrollo es necesaria para completamente diseñar estrategias neuroprotectoras, muchas de las cuales tendrán que comenzar in utero.

LESIÓN DE SUSTANCIA BLANCA Y DISMADURACIÓN DEL CEREBRO EN RN PRETÉRMINO

La lesión de la sustancia blanca (LSB) es la forma más común de injuria cerebral en neonatos prematuros y varía considerablemente en severidad. LSB comprende dos grupos mayores de patología: necrosis focal, que va desde lesiones quísticas hasta microscópicas y difusas no-necróticas (13). LSB está unida en modelos experimentales y estudios clínicos a isquemia, infección e inflamación (6). La necrosis quística focal, distintiva de la leucomalacia periventricular (LPV), se localiza en la sustancia blanca adyacente a los ventrículos. Estas grandes lesiones necróticas se han vuelto poco comunes en las cohortes contemporáneas de neonatos pretérmino, y la LSB difusa es ahora la lesión predominante en la mayoría de los neonatos prematuros. En los estudios de resonancia magnética (RMI), LSB aparece como áreas de anormalidades de la señal (14). Patológicamente, LSB difusa está marcada por lesión degenerativa y regeneración de preoligodendrocitos, una línea celular progenitora mitóticamente activa que hace su pico como línea celular entre las 23 y 32 semanas de gestación, y luego falla en madurar hacia oligodendrocitos productores de mielina (6). Hay algunas sugerencias de que la prevalencia de la LSB ha disminuido en las últimas dos décadas (15).

Figura. Conceptualización de la via de los trastornos placentarios a las alteraciones del neurodesarrollo.
SRIF= Síndrome de respuesta inflamatoria fetal.

En la RMI diagnóstica, LSB representa el aspecto más fácilmente percibido de las anormalidades del cerebro en neonatos prematuros. Sin embargo, no da completamente cuenta de la carga de discapacidad del neurodesarrollo en esta población (14). El desarrollo alterado de la sustancia blanca, las estructuras subcorticales, el cerebelo y la corteza contribuyen más a la discapacidad del neurodesarrollo después del nacimiento prematuro (9, 14). Entonces la dismaduración cerebral, más que la injuria, es la anormalidad cerebral primaria en las cohortes contemporáneas de neonatos prematuros (6). En la sustancia blanca, la detención del desarrollo de los preoligodendrocitos previene su maduración hacia oligodendrocitos mielinizantes y resulta en mielinización anormal. En la sustancia gris de los neonatos prematuros, la reducción en la arborización neuronal y la proliferación neuronal, más que la muerte neuronal, está implicada en la reducción del volumen cortical (6).

NACIMIENTO PREMATURO Y LA PLACENTA

Pese a que el nacimiento prematuro es visto con frecuencia como un proceso o resultado único, numerosos mecanismos biológicos, incluyendo variantes en loci genéticos maternos, llevan al parto prematuro (16, 17). Pese a esfuerzos significativos, estos pasos etiológicos son poco comprendidos y clasificados variablemente. El enfoque más básico clasifica el nacimiento prematuro como espontáneo o indicado. Sin embargo, este esquema falla al separar condiciones heterogéneas. Por ejemplo, el nacimiento prematuro en el contexto de hemorragia materna y RCF son ambos considerados "indicados", pero sus antecedentes y mecanismos son divergentes.

En 2009, un grupo de trabajo reunido por la Conferencia de la Global Alliance to Prevent Prematurity and Stillbirth (Alianza Global para prevenir la prematurez y muerte al nacer) propuso un sistema de clasificación basado en fenotipos clínicos más que en etiologías diferentes (16). Cada fenotipo fue definido por las características de la mujer gestante, el feto, la placenta, signos de parturición, y la forma de parto. Las características de la placenta incluyeron evidencia histológica de vasculitis/infarto/ necrosis y corioamnionitis histológica (16). Utilizando este concepto de fenotipo, los investigadores del NICHD buscaron agrupar el parto prematuro espontáneo en 9 potenciales fenotipos. Dos de los fenotipos más comunes fueron "infección/ inflamación" y "disfunción placentaria" (18). La mayoría de las mujeres (78%) tuvieron múltiples fenotipos. Interesantemente, ellos encontraron que las mujeres blancas tuvieron más insuficiencia placentaria que las mujeres no-blancas, y que la infección /inflamación estuvo asociada con parto prematuro espontáneo más temprano comparado con otros fenotipos. Sin embargo, no relacionaron el fenotipo con el posterior neurodesarrollo.

Es importante considerar el manejo antenatal de la mujer embarazada en riesgo de parto prematuro para promover la salud del cerebro del neonato prematuro. El manejo antenatal del parto prematuro previsto incluye corticosteroides, cuando el parto antes de 34 semanas de gestación se anticipa dentro de los siguientes 7 días, y sulfato de magnesio en las 24 horas previas al nacimiento. Dada la naturaleza sindrómica del parto prematuro, ambas terapias son prescriptas sin importar la enfermedad placentaria, y sus mecanismos protectores del cerebro son hasta cierto punto desconocidos.

INSUFICIENCIA PLACENTARIA

La insuficiencia placentaria es un fenotipo clínico ampliamente caracterizado por malperfusión vascular materna, isquemia placentaria e hipoxia crónica (19). Clínicamente, está asociada con 3 condiciones materno-fetales: preeclampsia, desprendimiento placentario, y RCF. Combinadas, estas 3 condiciones contribuyen a más de la mitad de los nacimientos prematuros por indicación médica (20).

Fisiopatológicamente, la insuficiencia placentaria resulta cuando las arterias en espiral maternas no desarrollan la reducción fisiológica en resistencia y el aumento del flujo necesario para perfundir el espacio intervelloso de la placenta (21). Al principio de la gestación, el trofoblasto remodela las arterias espiraladas uterinas en vasos altamente dilatados. La placenta juega un rol crítico en la oxigenación del feto y transporta metabolitos esenciales vía el circuito materno-fetal.

La insuficiencia placentaria, como una alteración de la función placentaria, no está definida por ninguna figura histopatológica. Más aún, no existe sistema de clasificación universalmente aceptado para las lesiones hipóxicas de la placenta. En 2016, un grupo de consenso de un workshop internacional (Grupo de Trabajo de la Placenta de Amsterdam) propuso un sistema abarcativo de clasificación que dicotomizó los procesos vasculares placentarios en malperfusión *materna* y *fetal* (22). A grosso modo, la malperfusión vascular materna está caracterizada por hipoplasia placentaria (peso de la placenta en percentilo ≤ 10 para la EG), infarto, y hemorragia retroplacentaria; microscópicamente, está caracterizada por hipoplasia vellosa distal y maduración vellosa acelerada para la EG. La edad placentaria acelerada para la gestación es pensada como una respuesta adaptativa a la hipoxia crónica, y la experiencia del patólogo es de vital importancia en identificar la hipermaduración placentaria (11, 23). La malperfusión vascular fetal posiblemente ocurre debido a obstrucción en el flujo sanguíneo fetal, y es caracterizada por trombosis y vellosidades segmentarias avasculares (22).

La ultrasonografía obstétrica puede prestar una visión dentro de la circulación uteroplacentaria y proveer una medida para la severidad de la insuficiencia placentaria. En los trimestres primero y segundo, el aumento de la impedancia en el flujo de las arterias uterinas, medido con velocimetría Doppler, predice la insuficiencia placentaria (24, 25). En los trimestres segundo y tercero, el flujo de la arteria umbilical correlaciona con la resistencia del flujo en la microcirculación placentaria. Las guías actuales recomiendan el uso del examen Doppler de la arteria umbilical en el marco de la sospecha de RCF, porque disminuye significativamente la posibilidad de inducción del parto, cesárea, y muertes perinatales (24, 26). En la medida que la insuficiencia placentaria empeora, el feto compensa desviando deliberadamente la sangre desde lechos vasculares no esenciales hacia el cerebro, y este fenómeno es manifestado por la resistencia reducida en las arterias cerebrales (27).

RCF se refiere a un feto que no ha alcanzado su potencial de crecimiento biológicamente determinado debido a un proceso patológico (28, 29). Las anomalías congénitas deberían estar ausentes al diagnosticar RCF. Una definición reciente de consenso de RCF clasificó el RCF temprano al instalado antes de las 32 semanas de gestación, y RCF tardío al que comienza a las 32 semanas o posterior, pero este aspecto de la definición ha sido aplicado inconsistentemente en los estudios (29). RCF

temprano, más que el tardío, es una preocupación clave en los neonatos prematuros, La mayoría, pero no todos, los neonatos nacidos después de RCF son PEG, definidos como tener PN menores al percentilo 10 para la EG y sexo. Importante, no todos los fetos nacidos PEG tienen RCF, y los estudios que igualan ambas poblaciones deben ser interpretados cuidadosamente. El feto responde a la hipoxia crónica enlenteciendo su ritmo de crecimiento y redistribuyendo el gasto cardíaco hacia el cerebro, corazón y adrenales (30). Contrario a su nombre "protección del cerebro" (brain sparing) en RCF no asegura neurodesarrollo normal. En efecto, la vasodilatación de la arteria cerebral media, la arteria cerebral más investigada en la ultrasonografía fetal clínica, refleja un estadio avanzado de malperfusión fetal y ocurre siguiendo la vasodilatación de otras arterias cerebrales (31). La protección del cerebro puede mitigar la injuria cerebral conservando la energía y preservando el flujo sanguíneo cerebral en regiones críticas, pero de ningún modo asegura neurodesarrollo típico. Después del RCF, los niños nacidos a término están en riesgo aumentado de déficit del neurodesarrollo y PC comparados con controles pareados sin RCF y niños nacidos PEG sin RCF (32, 33). Los niños nacidos PT después de RCF tienen mayor frecuencia de déficits cognitivos y de aprendizaje comparados con niños nacidos PT por otras razones (34, 35). En un estudio de una cohorte grande francesa de niños PT, aquellos nacidos PEG, que posiblemente representaban un grupo diluido de neonatos con RCF, tuvieron aproximadamente el doble de carga de dificultades cognitivas y escolares que aquellos nacidos apropiados para EG (34).

Los principales determinantes del resultado del neurodesarrollo en prematuros con RCF son la severidad de la insuficiencia placentaria (medida por ultrasonografía obstétrica), la EG al inicio del RCF, y la EG al nacer (36, 37). Los neonatos prematuros con RCF que manifiestan protección cerebral in utero están en riesgo aumentado para neurocomportamiento neonatal alterado comparado con aquellos con velocimetría anormal de la arteria umbilical aislada (38). En un subanálisis del Estudio de Flujo umbilical y fetal en Europa, que randomizó tempranamente fetos con dos estrategias de vigilancia, las anomalías del flujo sanguíneo cerebral fueron más predictivas de déficit del neurodesarrollo que las morbilidades clásicas neonatales (39). Como tal, al manejar RCF, el grado de compromiso in utero debe ser sopesado contra las exposiciones adversas asociadas con el nacimiento prematuro y el cuidado intensivo neonatal al adjudicar el mejor momento para el parto. El momento óptimo para el nacimiento de fetos con RCF y los mejores medios de vigilancia fetal son aún desconocidos (28, 40).

La lesión cerebral adquirida es común en fetos con RCF temprana (29, 41). En una serie prospectiva de un solo centro de 90 gestaciones con RCF con hallazgos anormales en el Doppler de la arteria umbilical y parto entre las 28 a 34 semanas de gestación, 40% tuvo injuria cerebral postnatal (ejemplo, HIV y LPV) comparado con 12% en controles pareados por EG adecuados para EG. Otra vez, aquellos con redistribución de la arteria

cerebral media tuvieron mayor riesgo de lesión cerebral (41). Sin embargo, estudios observacionales no reportan una asociación consistente entre HIV y RCF, con algunos sugiriendo que realmente el RCF es protector contra HIV en neonatos prematuros (42). En cuanto a la maduración cerebral, la sustancia gris parece ser particularmente vulnerable en neonatos prematuros con RCF. Estudios empleando RMN han mostrado que los RNPT con RCF volumen reducido de la sustancia gris cortical y discordancia de las circunvoluciones (43, 44). Estudios de neuropatología en neonatos con RCF han demostrado una reducción en el número de neuronas corticales relacionadas con controles (45). Más allá de la corteza, la mielinización de la sustancia blanca y los volúmenes del hipocampo y el cerebelo también están reducidos en prematuros con RCF (46).

Pocas opciones terapéuticas existen para reducir la injuria y dismaduración cerebral en neonatos prematuros nacidos luego de insuficiencia placentaria. La aspirina diaria en embarazos de alto riesgo de insuficiencia placentaria reduce la frecuencia de RCF y es actualmente recomendada en tales escenarios (28). En adición, cuando hay una real posibilidad de parto médicamente indicado antes de las 34 semanas de EG, están indicados los corticoides antenatales (28). En el marco de la insuficiencia placentaria, sin embargo, los efectos de los glucocorticoides antenatales son inciertos. Estudios retrospectivos, observacionales de neonatos PEG, muchos de los cuales fueron presumiblemente restringidos en crecimiento, han arrojado resultados conflictivos acerca de los efectos de los esteroides antenatales sobre los resultados mortalidad y neurodesarrollo (47). Fisiológicamente, varias líneas de razonamiento sugieren que neonatos PT con RCF pueden no beneficiarse de los esteroides antenatales en la misma medida que aquéllos sin RCF. Estos incluyen elevados niveles de esteroides endógenos en RCF; efectos negativos de los esteroides en el crecimiento y proliferación celular; y cambios en el flujo sanguíneo cerebral y umbilical conforme a que los esteroides antenatales pueden causar lesión por reperfusión (47). Otra potencial terapia en el futuro es la hiperoxigenación materna, que ha sido evaluada para el manejo del RCF temprano con resultados no concluyentes (48).

CORIOAMNIONITIS

La corioamnionitis aguda denota la presencia de la inflamación intra-amniòtica (49). Clínicamente, corioamnionitis aguda se refiere a una constelación de fiebre materna, taquicardia materna o fetal, dolor uterino, y líquido amniótico de olor fétido. Histopatológicamente, la corioamnionitis comprende la infiltración difusa de neutrófilos en la membrana corioamniótica. Corioamnionitis aguda *clínica* e *histológica* no son sinónimos, y aquí el término "corioamnionitis aguda" se referirá a la forma histológica. La tasa de corioamnionitis aguda están inversamente asociadas con la EG al nacer (12). La corioamnionitis se piensa que es infecciosa, con el microorganismo ascendiendo desde el tracto genital inferior o emergiendo por ruta hematógena. Sin

embargo, con frecuencia falta la evidencia de invasión bacteriana; entonces, la infección no es un requisito para el diagnóstico de corioamnionitis.

El trabajo de parto, a término o pretérmino, está caracterizado por cambios pro-inflamatorios en los tejidos gestacionales. Una diferencia clave es que la inflamación asociada con el parto prematuro es más intensa que la identificada en el parto de término (50). Para mejor comprender los orígenes de la corioamnionitis aguda, es importante apreciar los compartimientos anatómicos e inmunes de la placenta. Anatómicamente, la placenta puede ser dividida en el disco placentario, el corioamnios, y el cordón umbilical. Inmunológicamente, la respuesta inflamatoria de la placenta puede involucrar dos sistemas inmunes separados: 1) el materno, con neutrófilos ingresando al corioamnios vía venas deciduales (ej. Mucosa uterina) y la placa coriónica vía el espacio intervelloso, y 2) fetal, con neutrófilos ingresando al corioamnios y al cordón umbilical vía los vasos umbilicales y coriónicos (51). Del lado materno, la infiltración progresa desde el espacio intervelloso hacia el amnios; del lado fetal, progresa desde los vasos coriónicos y la vena umbilical a la arteria umbilical y la gelatina de Wharton. El sistema de estadificación del Grupo de Consenso de Amsterdam para ambas respuestas inflamatorias materna y fetal corresponde a esta progresión anatómica (22). La respuesta inflamatoria fetal también es llamada funisitis y puede estar acompañada por SRIF (síndrome de respuesta inflamatoria fetal) (22, 52). SRIF (FIRS en inglés) es definido como una respuesta fetal aguda sistémica inflamatoria a la corioamnionitis. La elevación de interleukina 6 en el cordón fetal, citokina inflamatoria circulante, es indicativa de SRIF. Debe notarse, que SRIF es posible en ausencia de infección microbiana, pero la respuesta más intensa está asociada con cultivo positivo de líquido amniótico (53).

Los estudios examinando la asociación entre corioamnionitis y la injuria de sustancia blanca y resultados en neurodesarollo en niños nacidos prematuros no son concluyentes (12). El ajuste de variables para factores de confusión incluyendo preeclampsia, y definición de variables de corioamnionitis (ejemplo, clínica vs. histológica) pueden explicar, al menos en parte, los hallazgos inconsistentes. Un meta-análisis original publicado en 2000 encontró que tanto la corioamnionitis clínica e histológica estuvieron asociadas con PC y LPV quística (54). Pese a que la mayoría de los estudios individuales no identificaron una asociación significativa, los datos agrupados encontraron a corioamnionitis como un factor de riesgo independiente para PC y LPV quística (RR de 1.6 y 2.1 respectivamente). Los más recientes meta-análisis publicados en 2017 distinguieron casos de término y pretérmino y enfoques de análisis prospectivo (determinando la tasa de PC en pacientes con y sin corioamnionitis) y retrospectivo (determinando la tasa de corioamnionitis en pacientes con y sin PC) (55). Estos autores reportaron una asociación entre corioamnionitis histológica y PC en niños en cohortes de prematuros (enfoque prospectivo). La asociación entre corioamnionitis clínica y PC estuvo limitada a cohortes de niños con PC (enfoque retrospectivo); los

resultados de los estudios empleando el enfoque retrospectivo son más susceptibles de distorsión por sesgo y confusores. Un estudio multicéntrico reciente que examinó la asociación entre corioamnionitis histológica y HIV, lesión de sustancia blanca, y posteriores scores cognitivos y motores encontró que una vez que los factores perinatales fueron incluídos en el modelo de regresión, la corioamnionitis no estaba fuertemente asociada con ninguno de los resultados (56). Desafortunadamente, pocos estudios han distinguido entre corioamnionitis afectando el lado fetal de la placenta, capaz de instigar SIRF, y afectando el lado materno. Un estudio reciente correlacionó la severidad de la funisitis con el déficit de neurodesarrollo, con funisitis necrotizante y vasculopatía coriónica severa estando asociado con la más alta frecuencia de déficit (57).

La corioamnionitis también ha sido asociada con la dismaduración de la sustancia blanca en algunos estudios pero no en otros (58, 59). La asociación entre corioamnionitis histológica y el desarrollo microestructural de la sustancia blanca a la edad equivalente al término independiente de los factores postnatales ha sido inconsistente, y si la dismaduración de la sustancia blanca comienza in utero requiere futura atención (58, 59). En un modelo en ratón de lesión de sustancia blanca perinatal, la inflamación sistémica moderada bloqueó la maduración de oligodendrocitos, resultando en déficits de mielinización persistentes (60). Mecanísticamente, SIRF puede contribuir a la dismaduración de la sustancia blanca, y posterior déficit del neurodesarrollo, vía citokinas proinflamatorias (12). Las citokinas pueden aumentar la permeabilidad de la barrera hemato-encefálica a la infiltración leucocitaria. Los preoligodendrocitos son particularmente vulnerables a la inflamación; insultos inflamatorios tales como la sepsis postnatal, displasia broncopulmonar y enterocolitis necrotizante están fuertemente asociados con la dismaduración de la sustancia blanca y posterior déficit (12). Una reducción de modificaciones epigenéticas a la línea de oligodendrocitos inducida por la inflamación puede predisponer a estos niños a mayor daño y prevenir la regeneración; recapitular los cambios epigenéticos del desarrollo podría ser un paso terapéutico viable en el futuro (61).

FUTURAS ÁREAS DE INVESTIGACIÓN

Para mitigar el daño asociado con la insuficiencia placentaria y la corioamnionitis, es necesaria una mejor comprensión de los antecedentes in utero de la dismaduración e injuria cerebral detectada postnatalmente. A tal efecto, el examen in utero del desarrollo (y mal desarrollo) de la placenta y el cerebro podría ayudar a dilucidar los orígenes placenta- mediante anterógrados de la dismaduración cerebral que precede a las exposiciones adversas en UCIN. La ultrasonografía, herramienta primaria para la evaluación de la placenta y el cerebro in utero, está limitada por el campo de visión y la resolución tisular. Técnicas avanzadas de RNM para la placenta y el cerebro fetal son prometedoras para identificar las consecuencias fisiopatológicas de la placenta alterada

(62, 63). La RNM de la placenta puede proveer importante información estructural y funcional en tiempo real para hacer preguntas de las múltiples facetas de la patología placentaria. Mapas aparentes de coeficiente- difusión pueden identificar y cuantificar áreas de difusión acelerada y restringida que corresponde a áreas de necrosis, infarto, o fibrosis en la placenta (64). La RNM del cerebro fetal podría identificar la dismaduración prenatal del cerebro, cuantificar el flujo sanguíneo cerebral fetal y la extracción de oxígeno y facilitar la optimización y el desarrollo de estrategias de neuroprotección fetal (10, 63). El desarrollo de la placenta artificial como un sistema de apoyo extrauterino agrega mayor urgencia para comprender la salud del cerebro in utero (65). La transición desde el vientre materno a la placenta artificial debería preferentemente ser lograda antes de que la salud cerebral esté en riesgo. La imagen cuantitativa del cerebro in utero podría ser utilizada para evaluar candidatos a ser transferidos desde el vientre materno a la placenta artificial. Más aún, la cuantificación intrauterina del flujo sanguíneo cerebral y la extracción de oxígeno por RNM podrían servir como biomarcadores de respuesta a las potenciales terapias.

En resumen, la RNM intraútero podría aislar los procesos que comienzan in utero, antes que ocurran los insultos postnatales, y elaborar los efectos de la malperfusión placentaria y la inflamación en relación a la salud cerebral.

CONCLUSIONES

La influencia de la placenta en la salud del cerebro de los neonatos prematuros es central para comprender los resultados del neurodesarrollo en esta población, y pide interacción más estrecha entre especialistas de medicina materno-fetal, neonatólogos y neurólogos. En neonatos prematuros, la insuficiencia placentaria y la corioamnionitis influencian el posterior neurodesarrollo, especialmente cuando ocurren a la vez (66). Tanto la insuficiencia placentaria, a través de inadecuada provisión de oxígeno y de nutrientes, y la corioamnionitis, vía SIRF, pueden contribuir a la dismaduración cerebral y la injuria y pueden establecer la base de contribuyentes postnatales de la salud cerebral. Imágenes avanzadas del cerebro pueden ser aplicadas en la actualidad para establecer los sustratos responsables, al menos en parte, para los resultados adversos del neurodesarrollo relacionados con estos ambientes hostiles intraútero. Al presenta, las terapias para atenuar la carga de déficit consiguiente a la mala perfusión e inflamación placentaria en el neonato prematuro son limitadas. Los avances en métodos de investigación, incluyendo imágenes cerebrales intraútero, proveen una oportunidad sin precedentes para identificar nuevas formas de mejorar la salud del cerebro de los neonatos prematuros, aún antes del nacimiento

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The Placenta and Neurodevelopment in Preterm Newborns

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Education Gaps

1. Clinicians should recognize that preterm neonates are at risk for neurodevelopmental impairment secondary to brain dysmaturation and injury.
2. Neonatal providers should understand the implications of placental insufficiency and chorioamnionitis on the neurodevelopment of preterm neonates.

Abstract

In caring for preterm neonates, a major challenge lies in understanding the contributors to brain dysmaturation and injury, both of which serve as precursors to childhood neurodevelopmental impairment. In addition to the various adverse exposures that the preterm newborn encounters in postnatal life, the placental antecedents of preterm delivery, in and of themselves, may affect brain dysmaturation and injury. The abnormal placenta is a frequent complication of pregnancy, and placental pathologies, such as placental insufficiency and acute chorioamnionitis, often precede preterm birth.

Placental insufficiency is the principal cause of fetal growth restriction and acts via chronic fetal hypoxia. During fetal hypoxia, cardiac output redistribution to the brain represents an important fetal adaptive response; however, vascular sparing of the brain does not ensure normal brain growth. Early fetal growth restriction, which is associated with a hypermature and malperfused placenta, results in neurodevelopmental impairment independent of the duration of gestation in preterm newborns. Acute chorioamnionitis is characterized by infiltration of the placenta by immune cells and often results from infection that induces an inflammatory response. Chorioamnionitis can lead to the fetal inflammatory response syndrome and preterm labor, and thus can add to subsequent neonatal brain injury. Placental health should be assessed in understanding the origins of preterm brain dysmaturation and injury, and subsequent neurodevelopmental impairment.

Objectives After completing this article, readers should be able to:

1. Describe the features of preterm brain dysmaturation and injury.

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ABBREVIATIONS

CP	cerebral palsy
FGR	fetal growth restriction
FIRS	fetal inflammatory response syndrome
IVH	intraventricular hemorrhage
MRI	magnetic resonance imaging
PVL	periventricular leukomalacia
WMI	white matter injury

2. Discuss the pathophysiology of brain sparing in placental insufficiency.
3. Describe the pathophysiology of the fetal inflammatory response syndrome in chorioamnionitis.

INTRODUCTION

Although survival rates of very preterm neonates have risen in recent decades, reflecting incremental advances in neonatal intensive care, preterm birth continues to be a leading cause of childhood and lifelong disability. (1) The World Health Organization estimates that approximately 15 million preterm infants (1 in 10 live births) are born at less than 37 weeks' gestation worldwide every year. Among survivors of very preterm birth, which is defined as birth at less than or equal to 32 weeks, approximately 5% to 10% have major motor deficits such as cerebral palsy (CP) but a much greater proportion have cognitive, behavioral, or sensory disorders that manifest later in childhood. (2)(3) These relatively mild deficits result in academic difficulties and persist into adulthood. (4)(5) The social and economic burden of preterm birth is, therefore, considerable.

Over the last decade, the vulnerability of the preterm brain is increasingly being recognized as a problem of *dysmaturation* rather than exclusively of necrotic injuries. (6) Many groups have shown that aspects of the preterm neonate's postnatal course—including mechanical ventilation, infections, malnutrition, and painful procedures—contribute to brain dysmaturation. (7)(8)(9) Nonetheless, given that preterm birth is a syndrome that is often attributed to placental pathologies, the brain dysmaturation that leads to later neurodevelopmental impairments may have its origins in perturbed in utero physiology. There is compelling evidence that the brain of the fetus that will subsequently be born preterm is functionally altered relative to that of the fetus that will subsequently be born at term. (10) In a first-of-its-kind study of 36 pregnant women, Thomason et al showed that brain connectivity was diminished in fetuses that were subsequently born preterm, suggesting that neurodevelopmental impairment after preterm birth may have in utero origins. (10) In other words, the brain of the fetus destined to be born preterm may deviate from its normal developmental trajectory, presumably related at least in part, to the in utero environment that will eventually lead to preterm birth.

The placenta is the key tissue regulating the fetal environment, mediating the exchange of nutrients and waste products between the maternal and fetal circulations. Placental disturbances are found in many antenatal conditions that lead to preterm birth and may contribute to poor neurodevelopment (Figure). These disturbances can be broadly classified as the malperfused placenta and the inflamed placenta. The malperfused placenta, as in placental insufficiency, is a common precursor to fetal growth restriction (FGR) and preeclampsia, both of which can precede and complicate preterm birth. (11) The inflamed placenta, as in acute chorioamnionitis, is a trigger for preterm labor, and can lead to the fetal inflammatory response syndrome (FIRS) through the release of proinflammatory cytokines. (12)

A better understanding of the relationship between the placenta and neurodevelopment is necessary to fully exploit neuroprotective strategies, many of which need to begin in utero.

WHITE MATTER INJURY AND BRAIN DYSMATURATION IN PRETERM NEONATES

White matter injury (WMI) is the most common form of brain injury in preterm neonates and varies considerably in severity. WMI encompasses 2 major groups of pathology: focal necrosis, which ranges from cystic to microscopic,

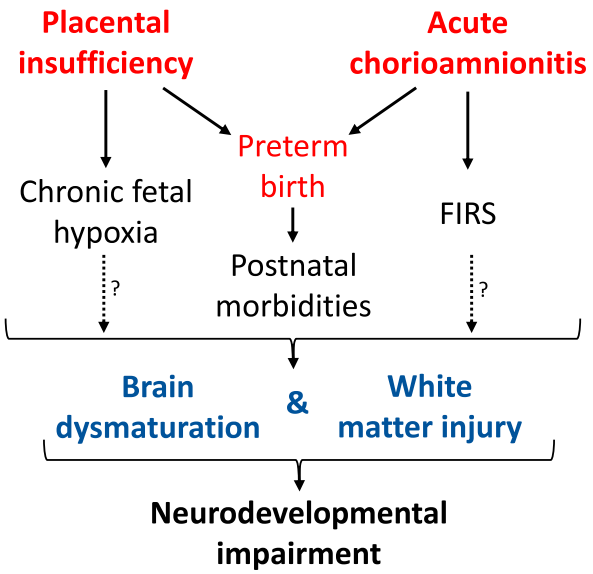

Figure. Conceptualization of the pathway from placental disturbances to neurodevelopmental impairment. FIRS=fetal inflammatory response syndrome.

and diffuse non-necrotic lesions. (13) WMI is linked in experimental models and clinical studies to ischemia, infection, and inflammation. (6) Focal cystic necrosis, the hallmark of periventricular leukomalacia (PVL), localizes to the white matter adjacent to the ventricles. These large necrotic lesions have become uncommon in contemporary cohorts of preterm neonates, and diffuse WMI is now the predominant lesion in most preterm neonates. On diagnostic magnetic resonance imaging (MRI) scans, WMI appears as areas of signal abnormalities. (14) Pathologically, diffuse WMI is marked by selective degeneration and regeneration of preoligodendrocytes, a mitotically active progenitor cell line that peaks as a cell line between 23 and 32 weeks' gestation, and then fails to mature to myelin-forming oligodendrocytes. (6) There is some suggestion that the prevalence of WMI has decreased over the last 2 decades. (15)

On diagnostic MRI, WMI represents the most easily perceived aspect of brain abnormalities in preterm neonates. However, it does not fully account for the burden of neurodevelopmental disability in this population. (14) Impaired *development* of the white matter, subcortical structures, cerebellum, and the cortex contribute more to neurodevelopmental disability after preterm birth. (9) (14) Thus, brain dysmaturation, rather than injury, is the primary brain abnormality in contemporary cohorts of preterm neonates. (6) In the white matter, developmental arrest of preoligodendrocytes prevents their maturation into myelinating oligodendrocytes and results in abnormal myelination. In the grey matter of preterm neonates, reduction in neuronal arborization and neuronal proliferation, rather than neuronal death, is implicated in reduced cortical volume. (6)

PRETERM BIRTH AND THE PLACENTA

Although preterm birth is often viewed as a single process or outcome, numerous biological mechanisms, including variants in maternal genetic loci, lead to preterm birth. (16)(17) Despite significant efforts, these etiologic pathways are poorly understood and variably classified. The most basic approach classifies preterm birth as either spontaneous or indicated. However, this schema fails to separate heterogeneous conditions. For example, preterm birth in the context of maternal hemorrhage and FGR are both considered indicated, but their antecedents and mechanisms are divergent.

In 2009, a working group brought together by the Global Alliance to Prevent Prematurity and Stillbirth Conference proposed a classification system that was based on clinical phenotypes rather than distinct etiologies. (16) Each phenotype was defined by characteristics of the pregnant woman, the fetus, the placenta, signs of parturition, and the pathway to delivery. Placental characteristics included *histologic evidence of vasculitis/infarction/necrosis* and *histologic chorioamnionitis*. (16) Using this concept of phenotype, investigators at the National Institute of Child Health and Human Development sought to group spontaneous preterm birth into 9 potential phenotypes. Two of the more common phenotypes were "infection/inflammation" and "placental dysfunction." (18) The majority of women (78%) had multiple phenotypes. Interestingly, they found that white women had more placental insufficiency than nonwhite women, and that infection/inflammation was associated with earlier spontaneous preterm birth compared with other phenotypes. However, they did not relate the phenotypes to later neurodevelopment.

It is important to consider the antenatal management of the pregnant woman at risk for preterm delivery in promoting brain health in the preterm neonate. The antenatal management of expectant preterm birth includes corticosteroids, when delivery at less than 34 weeks' gestation is anticipated within 7 days, and magnesium sulfate in the 24 hours before preterm delivery. Given the syndromic nature of preterm birth, both therapies are prescribed regardless of placental disease, and their brain-protective mechanisms are to some extent unknown.

PLACENTAL INSUFFICIENCY

Placental insufficiency is a clinical phenotype broadly characterized by maternal vascular malperfusion, placental ischemia, and chronic hypoxia. (19) Clinically, it is associated with 3 maternal-fetal conditions: preeclampsia, placental abruption, and FGR. Combined, these 3 conditions contribute to over half of medically indicated preterm births. (20) Pathophysiologically, placental insufficiency results when the maternal spiral arteries do not undergo the physiologic reduction in resistance and increase in flow necessary to perfuse the intervillous space of the placenta. (21) Early in pregnancy, the invading trophoblast remodels the uterine spiral arteries into highly dilated vessels. The placenta plays a critical role in oxygenation of the fetus and transports essential metabolites via the maternal-fetal circuit.

Placental insufficiency, as a disorder of placental function, is not defined by any single histopathologic feature. Furthermore, there is no universally accepted classification system for placental hypoxic lesions. In 2016, a consensus group from an international workshop (the Amsterdam

Placental Workshop Group) proposed a comprehensive classification system that dichotomized placental vascular processes into *maternal* and *fetal* vascular malperfusion. (22) Grossly, maternal vascular malperfusion is characterized by placental hypoplasia (placental weight ≤10th percentile for gestational age), infarction, and retroplacental hemorrhage; microscopically, it is characterized by distal villous hypoplasia and accelerated villous maturation for gestational age. Accelerated placental age for gestation is thought to be an adaptive response to chronic hypoxia, and the experience of the pathologist is of vital importance in identifying placental hypermaturation. (11)(23) Fetal vascular malperfusion likely occurs because of obstruction in fetal blood flow, and is characterized by thrombosis and segmental avascular villi. (22)

Obstetric ultrasonography can lend insight into the uteroplacental circulation and provide a measure for the severity of placental insufficiency. In the first and second trimesters, increased impedance to flow in the uterine arteries, as measured with Doppler velocimetry, predicts placental insufficiency. (24)(25) In the second and third trimesters, umbilical artery flow correlates with downstream resistance in the placental microcirculation. Current guidelines recommend the use of umbilical arterial Doppler assessment in the setting of suspected FGR, because it significantly decreases the likelihood of labor induction, cesarean delivery, and perinatal deaths. (24)(26) As placental insufficiency worsens, the fetus compensates by deliberately shunting blood away from nonessential vascular beds toward the brain, and this phenomenon is manifested by reduced resistance in the cerebral arteries. (27)

FGR refers to a fetus that has not attained its biologically determined growth potential because of a pathologic process. (28)(29) Congenital anomalies should be absent when diagnosing FGR. A recent consensus definition of FGR classified early FGR as having its onset before 32 weeks' gestation and late FGR as beginning at 32 weeks' or later, but this aspect of the definition has been inconsistently applied across studies. (29) Early FGR, rather than late, is a key concern in preterm neonates. Most, but not all, neonates born after FGR are small for gestational age, defined as having birthweights less than the 10th percentile for gestational age and sex. Importantly, not all fetuses born small for gestational age have FGR, and studies that equate the 2 populations need to be carefully interpreted. The fetus responds to chronic hypoxia by slowing its growth rate and redistributing cardiac output to the brain, heart, and adrenals. (30) Contrary to its name, "brain sparing" in FGR does not ensure normal neurodevelopment. In fact, vasodilation of the middle cerebral artery, the most commonly investigated cerebral artery in clinical fetal ultrasonography, reflects an advanced stage of fetal malperfusion and occurs following vasodilation of the other cerebral arteries. (31) Brain sparing may mitigate brain injury by conserving energy and preserving cerebral blood flow in critical regions, but it by no means ensures typical neurodevelopment. After FGR, children born at term are at increased risk for neurodevelopmental impairment and CP compared with both matched controls without FGR and children born small for gestational age with absent FGR. (32)(33) Children born preterm after FGR have a higher frequency of cognitive and learning deficits compared with children born preterm for other reasons. (34)(35) In a large French cohort study of preterm children, those born small for gestational age, which likely represented a diluted group of FGR neonates, had approximately twice the burden of cognitive and school difficulties than those born appropriate for gestational age. (34)

The main determinants of neurodevelopmental outcome in preterm FGR are the severity of placental insufficiency (as measured on obstetric ultrasonography), the gestational age at onset of FGR, and the gestational age at delivery. (36)(37) Preterm neonates with FGR who manifest in utero brain sparing are at increased risk for neonatal neurobehavioral impairment compared with those with abnormal umbilical arterial velocimetry in isolation. (38) In a subanalysis of the Trial of Umbilical and Fetal Flow in Europe, which randomized early FGR fetuses to 2 surveillance strategies, cerebral blood flow anomalies were more predictive of neurodevelopmental impairment than classic neonatal morbidities. (39) As such, in managing FGR, the degree of in utero compromise must be weighed against the adverse exposures associated with preterm delivery and neonatal intensive care in adjudicating the best time for delivery. The optimal timing for the delivery of fetuses with FGR and best means of fetal surveillance are still unknown. (28)(40)

Acquired brain injury is common in fetuses with early-onset growth restriction. (29)(41) In a prospective single center series of 90 FGR pregnancies with abnormal umbilical artery Doppler findings and delivery at 28 to 34 weeks' gestation, 40% had postnatal brain injury (ie, intraventricular hemorrhage [IVH] and PVL) compared with 12% in gestational age–matched appropriate for gestational age controls. Again, those with middle cerebral artery redistribution were at an elevated risk for brain injury. (41) Nonetheless, observational studies do not report a consistent association between IVH and FGR, with some actually suggesting that FGR is protective against IVH in preterm neonates. (42) With regard to brain maturation, the grey

matter seems to be particularly vulnerable in preterm FGR neonates. Studies using MRI have shown that preterm neonates with FGR have reduced cortical grey matter volume and discordant gyrification. (43)(44) Neuropathology studies of neonates with FGR have demonstrated a reduction in the number of cortical neurons relative to controls. (45) Beyond the cortex, white matter myelination and hippocampal and cerebellar volumes are also reduced in preterm FGR. (46)

Few therapeutic options exist to reduce brain injury and dysmaturation in preterm neonates born following placental insufficiency. Daily aspirin in pregnancies at high risk for placental insufficiency reduces the frequency of FGR and is currently recommended in such scenarios. (28) In addition, when there is a real possibility of medically indicated delivery before 34 weeks' gestation, antenatal corticosteroids are indicated. (28) In the setting of placental insufficiency, however, the effects of antenatal glucocorticoids are uncertain. Observational, retrospective studies of small-for–gestational age neonates, many of whom were presumably growth restricted, have yielded conflicting results about the effects of antenatal steroids on mortality and neurodevelopmental outcomes. (47) Physiologically, several lines of reasoning suggest that FGR preterm neonates may not benefit from antenatal steroids to the same extent as those without FGR. These include elevated levels of endogenous steroids in FGR; negative effects of steroids on growth and cellular proliferation; and changes in umbilical and cerebral blood flow pursuant to antenatal steroids that may cause reperfusion injury. (47) Another potential future therapy is maternal hyperoxygenation, which has been evaluated for the management of early FGR with inconclusive results. (48)

CHORIOAMNIONITIS

Acute chorioamnionitis denotes the presence of intra-amniotic inflammation. (49) Clinically, acute chorioamnionitis refers to the constellation of maternal fever, maternal or fetal tachycardia, uterine tenderness, and foul-smelling amniotic fluid. Histopathologically, chorioamnionitis comprises diffuse infiltration of neutrophils into the chorioamniotic membrane. *Clinical* and *histologic* acute chorioamnionitis are not synonymous, and herein the term "acute chorioamnionitis" will refer to the histologic form. The rates of acute chorioamnionitis are inversely associated with gestational age at delivery. (12) Chorioamnionitis is thought to be infectious, with the microorganism ascending from the lower genital tract or emerging via the hematogenous route. However, evidence of microbial invasion is often lacking; therefore, infection is not a requisite for the diagnosis of chorioamnionitis.

Labor, be it term or preterm, is characterized by proinflammatory changes in gestational tissues. A key difference is that the inflammation associated with preterm labor is more intense than that identified in term parturition. (50) To better understand the origins of acute chorioamnionitis, it is important to appreciate the anatomic and immune compartments of the placenta. Anatomically, the placenta can be divided into the placental disc, the chorioamnion, and the umbilical cord. Immunologically, the placenta's inflammatory response can involve 2 separate immune systems: 1) maternal, with neutrophils entering the chorioamnion via decidual (ie, uterine mucosal) venules and the chorionic plate via the intervillous space, and 2) fetal, with neutrophils entering the chorioamnion and the umbilical cord via umbilical and chorionic vessels. (51) On the maternal side, the infiltration progresses from the subchorionic intervillous space to the amnion; on the fetal side, it progresses from the chorionic vessels and umbilical vein to the umbilical artery and Wharton jelly. The Amsterdam Placental Workshop Group Consensus Statement staging system for both the maternal and fetal inflammatory responses corresponds to this anatomic progression. (22) The fetal inflammatory response is also termed *funisitis* and can be accompanied by FIRS. (22)(52) FIRS is defined as an acute fetal systemic inflammatory response to chorioamnionitis. Elevated fetal cord interleukin 6, a circulating inflammatory cytokine, is indicative of FIRS. Of note, FIRS is possible in the absence of microbial infection, but the most intense response is associated with a culture-positive amniotic infection. (53)

Studies examining the association between chorioamnionitis and WMI and neurodevelopmental outcomes in children born preterm are inconclusive. (12) Variable adjustment for confounding factors including preeclampsia, and variable definitions of chorioamnionitis (ie, clinical vs histologic) may explain, at least in part, the inconsistent findings. An original meta-analysis published in 2000 found that both clinical and histologic chorioamnionitis were associated with CP and cystic PVL. (54) Although most individual studies did not identify a significant association, the pooled data found chorioamnionitis to be an independent risk factor for both CP and cystic PVL (relative risk of 1.6 and 2.1, respectively). The most recent meta-analysis published in 2017 distinguished preterm and term cases and forward (determining the rate of CP in patients with and without chorioamnionitis) and backward (determining the rate of chorioamnionitis in patients with and without CP) approaches to analysis. (55) These authors reported an association between histologic chorioamnionitis and CP

in children in preterm cohorts (ie, forward approach). The association between clinical chorioamnionitis and CP was limited to cohorts of children with CP (ie, backward approach); results from studies using the backward approach are more susceptible to distortion from bias and confounding. A recent multicenter study examining the association between histologic chorioamnionitis and IVH, WMI, and later cognitive and motor scores found that once perinatal factors were accounted for in the regression model, chorioamnionitis was not strongly associated with any of the outcomes. (56) Unfortunately, few studies have distinguished between chorioamnionitis affecting the fetal side of the placenta, capable of instigating FIRS, and that affecting the maternal side. One recent study correlated the severity of funisitis with neurodevelopmental impairment, with necrotizing funisitis and severe chorionic vasculopathy being associated with the highest frequency of impairment. (57)

Chorioamnionitis has also been linked to white matter dysmaturation in some studies but not others. (58)(59) The association between histologic chorioamnionitis and white matter microstructural development at term-equivalent age independent of postnatal factors has been inconsistent, and whether white matter dysmaturation begins in utero requires further attention. (58)(59) In a mouse model of perinatal WMI, moderate systemic inflammation blocked oligodendrocyte maturation, resulting in persistent myelination defects. (60) Mechanistically, FIRS may contribute to white matter dysmaturation, and later neurodevelopmental impairment, via proinflammatory cytokines. (12) The cytokines can increase the permeability of the blood-brain barrier to leukocyte infiltration. Preoligodendrocytes are particularly vulnerable to inflammation; inflammatory insults such as postnatal sepsis, bronchopulmonary dysplasia, and necrotizing enterocolitis are strongly associated with white matter dysmaturation and later impairment. (12) A reduction in epigenetic modifications to the oligodendrocyte lineage induced by inflammation may predispose these children to further damage and prevent regeneration; recapitulating developmental epigenetic changes could be a viable therapeutic pathway in the future. (61)

FUTURE AREAS FOR RESEARCH

To mitigate the harm associated with placental insufficiency and chorioamnionitis, a better understanding of the in utero antecedents of postnatally detected brain dysmaturation and injury is needed. To that effect, in utero assessment of placental and brain development (and maldevelopment) could help elucidate the upstream, placenta-mediated origins of brain dysmaturation that precede adverse exposures in the NICU. Ultrasonography, the primary tool for placental and brain evaluation in utero, is limited by field of view and tissue resolution. Advanced MRI techniques for the placenta and fetal brain hold promise in identifying the pathophysiologic consequences of the disordered placenta. (62)(63) MRI of the placenta can provide important real-time structural and functional information to interrogate the multiple facets of placental pathology. Apparent diffusion-coefficient maps can identify and quantify areas of accelerated and restricted diffusion that correspond to areas of necrosis, infarction, or fibrosis in the placenta. (64) Fetal brain MRI could identify prenatal brain dysmaturation, quantify fetal cerebral blood flow and oxygen extraction, and facilitate the optimization and development of fetal neuroprotective strategies. (10)(63) The development of the artificial placenta as an extrauterine support system adds more urgency to understanding in utero brain health. (65) Transfer from the womb to the artificial placenta would preferably be accomplished before brain health is put at risk. In utero quantitative brain imaging could be used to evaluate candidates for transfer from the womb to the artificial placenta. Furthermore, in utero quantification of cerebral blood flow and oxygen extraction by MRI could serve as biomarkers for response to potential therapies.

In summary, in utero MRI could isolate processes that begin in utero, before postnatal insults occur, and elaborate the effects of placental malperfusion and inflammation as they relate to brain health.

CONCLUSIONS

The influence of the placenta on the brain health of preterm neonates is central to understanding the neurodevelopmental outcomes in this population, and calls for closer interaction between fetal-maternal medicine specialists, neonatologists, and neurologists. In preterm neonates, placental insufficiency and chorioamnionitis influence later neurodevelopment, especially when they occur together. (66) Both placental insufficiency, via inadequate oxygen and nutrient delivery, and chorioamnionitis, via FIRS, may contribute to brain dysmaturation and injury and may establish a foundation for postnatal contributors to brain health. Advanced brain imaging can now be applied to establish the substrates responsible, at least in part, for the adverse neurodevelopmental outcomes related to these hostile in utero environments. At present, therapies to attenuate the burden of impairment consequent to placental malperfusion and inflammation in the preterm neonate are

limited. Advances in research methods, including in utero brain imaging, provide an unprecedented opportunity to identify new ways to improve the brain health of preterm neonates, even before delivery.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the complications and effects of chorioamnionitis in the mother and the fetus.
- Know the causes and pathophysiology, including cellular abnormalities, of chronic asphyxia syndromes (eg, chronic fetal hypoxia and placental insufficiency).
- Know the risks of neurodevelopmental impairments in term infants, late preterm infants, moderately preterm infants, and extremely preterm infants, with and without neurologic risk factors.

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1. A female preterm infant born at 25 weeks' gestational age is now 14 weeks old. She received mechanical ventilation for 2 weeks in the initial newborn period, had feeding intolerance with slow advancement, but is now tolerating feedings. The infant has poor oral feeding ability and also has abnormalities on neurologic examination. A magnetic resonance imaging scan of the brain reveals some white matter injury. Which of the following correctly describes this type of injury?
    A. White matter injury is the most common form of brain injury in preterm infants.
    B. Large necrotic lesions adjacent to the ventricles are the most common manifestation.
    C. White matter injury reflects necrosis of fully developed oligodendrocytes.
    D. White matter injury is closely linked to ischemia, but not to infection or inflammation.
    E. Although white matter injury can sometimes be seen on magnetic resonance imaging, the optimal imaging modality is ultrasonography.
2. A male fetus is being followed for growth restriction. He is delivered at 30 weeks' gestational age because of ongoing concerns for growth restriction and placental insufficiency. The placenta is examined by the pathologist. Which of the following is most likely to be a finding?
    A. Larger than average placental size accounted for by overcompensation of blood flow.
    B. Distal villous hyperplasia and hypertrophy.
    C. Retroplacental hemorrhage and infarction.
    D. Characteristics of immature and undeveloped placenta.
    E. A consistent finding of velamentous cord insertion.
3. A woman who had preeclampsia and preterm birth in her prior pregnancy is receiving prenatal care for a subsequent pregnancy. She is receiving serial ultrasound evaluations. Which of the following findings are consistent with relatively severe placental insufficiency?
    A. Normal blood flow and normal placental appearance during the first and second trimesters.
    B. Decreased impedance to flow in the uterine arteries.
    C. No significant findings on umbilical arterial Doppler assessment.
    D. Increased resistance in fetal cerebral arteries.
    E. Shunting of blood away from nonessential vascular beds toward the fetal brain.
4. A male fetus is being followed for growth restriction. The mother is receiving close follow-up for prenatal care and serial ultrasound evaluations. Which of the following statements concerning fetal growth restriction is correct?
    A. Fetal growth restriction is synonymous with small for gestational age.
    B. When the brain is "spared" from growth restriction, there can be reassurance with regard to normal neurodevelopment.
    C. Children born preterm after fetal growth restriction have a higher frequency of cognitive and learning deficits compared with children born preterm for other reasons.
    D. Aspirin given in the context of placental insufficiency can exacerbate bleeding risk and increase the severity of growth restriction.
    E. The growth-restricted fetus preferentially redistributes cardiac output primarily to the kidneys, leading to oligohydramnios.

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5. A pregnant woman presents in preterm labor at 28 weeks of gestation. She receives tocolytics and steroids, but proceeds to deliver her infant the day after admission. On pathologic examination, the placenta is noted to have histologic evidence suggesting chorioamnionitis. Which of the following statements concerning this diagnosis is correct?
    A. Documented maternal or neonatal fever is necessary to confirm a diagnosis of chorioamnionitis.
    B. The rates of acute chorioamnionitis are inversely associated with gestational age at delivery.
    C. Evidence of microbial invasion in histology is necessary for a true diagnosis of chorioamnionitis.
    D. The primary histologic finding in chorioamnionitis is infiltration of the placenta by maternal lymphocytes and monocytes.
    E. Chorioamnionitis has been associated with white matter brain injury and cerebral palsy, but only in the context of term births, not preterm births.

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