Seguimiento del Neurodesarrollo en infantes Pre-término

¿Qué hay de nuevo?

Elisabeth C. McGowan, Betty R. Vohr

PALABRAS CLAVE

- Neurodesarrollo • Parálisis cerebral • Infantes prematuros
- Alteración del desarrollo de la coordinación • Lenguaje • **Nivel socioeconómico**

PUNTOS CLAVE

- Pese a que la tasa de parálisis cerebral (PC) ha disminuido entre infantes prematuros, la tasa de PC leve y la identificación del desorden de desarrollo de la coordinación (DDC) ha aumentado en esta población.
- Se ha mostrado que DDC tiene efectos persistentes en la edad escolar y adolescencia
- Aumenta el reconocimiento de la importancia de la exposición temprana a lenguaje interactivo en el desarrollo del lenguaje de los infantes.
- Pese a que el nivel de educación materna continúa siendo el indicador de nivel socioeconómico más frecuentemente reportado, hay creciente evidencia del impacto de las adversidades socioeconómicas en el neurodesarrollo pretérmino y resultados conductuales.
- La identificación de salud mental materna adversa un la UCIN y postalta provee una oportunidad de intervención en pacientes ex prematuros y sus madres.

Hay creciente evidencia de los cambios que ocurren a corto y largo plazo en los resultados del desarrollo motor y de lenguaje en la población pretérmino. Además, hay aumento de la preocupación acerca del impacto negativo de las adversidades psico-socio-económicas en los resultados de prematuros. Esta revisión provee actualizaciones en 3 áreas de cambios reportados en el seguimiento del neurodesarrollo y resultados en infantes pretérmino: déficits motores, retrasos y desórdenes del lenguaje, y el impacto de adversidades psico-socio-económicas de la familia en los resultados.

DÉFICITS MOTORES ENTRE INFANTES PRETÉRMINO- UN CUADRO CAMBIANTE

El cuidado intensivo neonatal moderno ha contribuido al aumento de la sobrevida de infantes en el límite de la viabilidad (1-4), y cambios en las tasas de morbilidades neonatales (5) y déficits del neurodesarrollo (1, 3). Un componente clave del déficit del neurodesarrollo es la parálisis cerebral (PC) (6). En los primeros años de la Neonatología, un foco primario de los estudios de seguimiento estuvo en la identificación de las tasas de PC (7-9). PC está con frecuencia asociada con otras secuelas a largo plazo, incluyendo déficits cognitivos, sensoriales, y del lenguaje; desórdenes convulsivos; y anormalidades del crecimiento. Es difícil lograr la confirmación de este diagnóstico antes de los 18 a 24 meses de edad, especialmente si la manifestación es leve. La categorización del grado de severidad de la PC basada en el Gross Motor Classification System (10) en leve (nivel 1), moderada (niveles 2 y 3), y severa a profunda (niveles 4 y 5) es bien aceptada.

Estudios recientes sugieren cambios en las tasas de PC y en el grado de severidad (5, 11-14). El estudio de la Neonatal Research Network (NRN) de infantes prematuros con edad gestacional menor o igual a 27 semanas, nacidos entre 2011 y 2014 y evaluados hasta los 18 a 26 meses de edad mostró que la tasa de PC disminuyó durante este período de 16% a 12% (5). Además, mientras que la tasa de PC severa disminuyó en 43%, la tasa de PC leve aumentó un 13% durante el período en estudio. Un 19& adicional tuvo un examen neurológico sospechoso. Esto indica que está ocurriendo una mejora en los resultados motores en conjunción con el aumento de sobrevida de los neonatos más prematuros. Este hallazgo apoya que así como hay un espectro de anormalidades de la sustancia blanca entre los infantes prematuros, hay un espectro o un continuo de hallazgos motores que van desde leves a profundos (15, 16).

Los infantes ex prematuros están en riesgo de una variedad de anormalidades motoras, incluyendo hitos motores demorados, anormalidades del balance, desafíos en la destreza manual, y anormalidades de la coordinación generalizada ahora codificada como desorden del desarrollo de la coordinación (DDC) con la Movement Assessment Battery for Children (MABC)-Segunda Edición (MABC- 2) (17-19). La Asociación Americana de Psiquiatría en 2013 definió DDC como un déficit en las habilidades motoras de coordinación que interfiere significativamente con el desempeño en las actividades de la vida diaria. Las habilidades investigadas incluyen destreza manual, intención, y ataje y balance. Los scores > percentil 15 son considerados normales, scores entre percentilos 6 a 15 están en riesgo, y scores menor o igual a percentilo 5 son consistentes con significativa dificultad motora. Pese a que las demoras en el desarrollo motor son evidentes en la infancia temprana, el diagnóstico de DDC con frecuencia no es hecho hasta la edad escolar (20). Una serie de estudios reportando DDC a los 3 años a 24 años se muestra en la TABLA 1.

Tabla 1
Desorden de la coordinación del desarrollo

Autores, Año Publicado	Edad Gestacional	Fecha de nacimiento o de las visitas	Tamaño de la muestra	Edad de evaluación	Evaluación de Movimiento Batería para Trastorno de Coordinación en Niños	
Kwork y Cols, 2018 Canadá	24-32 SDG	visitas 2010-2015	165	3 a. 4.5 a	Predicción Sensibilidad Especificidad	 90% 69%
Griffiths y Cols, 2017 Australia	<30 SDG	2005-2007	96	 4 a 8 a	< 5º percentil % (calificación) 25º % 25º %	
Bolk y Cols 2018 Suecia	22-26 SDG	Nacimiento 2004-2007	229 preterm 224 término	6.5 a	<5º% Pretérmino Término	 37% 5.5%
Davis y Cols, 2007 Australia: Grupo de estudio colaborativo Victoriano	22-27 SDG	Nacimiento 1991-1992	163	8 a	<15º % <5º %	10% 2%
Roberts 2011 Australia Grupo de estudio colaborativo Victoriano	22-27 SDG	1997	132 154 término	8 a	Premat <15º % Premat <5º % Termino < 5º %	10% 16% 5%
Spittle y cols, 2018 Australia Grupo de estudio colaborativo Victoriano	22-27 SDG	Año de estudio 1991-1992 1997 2005	 226 172 189	8 a	<5º % <5º % <5º %	2% 8% 7%
Setanen y cols, 2016 PIPARI Grupo de Estudio de Finlandia	23-35 SDG	2001-2004	82	11 a	<5º %	8%
Husby y cols, 2013 Noruega	MBPN* <1500 g	1986-1988	36 MBPN 37 Termino	14 a 23 a	<5º % <5º %	29% 29%

Kwok y colegas (21) examinaron el valor predictivo de la MABC-2 a los 3 años para predecir DDC a los 4.5 años en infantes muy pretérmino (MPT), definidos por los investigadores como 24 a 32 semanas de EG, y reportaron una sensibilidad de 90% y especificidad de 69%, indicando muchos resultados falsos positivos. Los investigadores concluyeron que a esta temprana edad, la MABC es altamente sensible pero con limitada especificidad para identificar niños MPT que tuvieron riesgo de DDC. El estudio de Griffiths y colegas (22) reportó que 25% de los infantes nacidos menores de 30 semanas de EG tuvieron scores consistentes con significativa dificultad motora (≤5%) a los 4 años y a los 8 años de edad y el MABC-2 a los 4 años tuvo alta sensibilidad (79%) y especificidad (93%) para predecir déficit motor a los 8 años. Bolk y colegas (23) examinaron una extensa cohorte de infantes EPT (22-26 semanas de EG) comparados con controles de término a los 6.5 años de edad y reportaron la tasa más alta de DDC de 37.1% en infantes PT versus 5.5 % en infantes de término. Tres estudios del Victorian Infant Collaborative Study Group (24) de infantes nacidos entre las 22 a 27 semanas de EG identificaron consistentemente tasas bajas pero en aumento de 2%, 8%, y 7%. Los hallazgos son similares a aquellos de Setanen y colegas (25% in una cohorte finlandesa a los 11 años de edad. Finalmente, un estudio (26) de Noruega reportó tasas de DDC de 29% en una pequeña cohorte de infantes ex MBPN, <1500 g, nacidos desde 1986 a las edades de 14 y 23 años. A los 23 años, los niños MBPN tuvieron scores motores totales y subscores de destreza manual y balance más pobres comparados con el grupo de comparación de término. Después de excluir 4 sujetos MBPN con PC, sin embargo, la diferencia en el score total del MABC-2) no continuó siendo significativa (26). Este estudio tiene un tamaño muestral pequeño y los resultados necesitan ser replicados en estudios mayores. Los porcentajes identificados en los reportes son influidos si los niños con PC son excluidos (27). Los hallazgos en general sugieren que los desafíos en la coordinación motora temprana entre infantes exprematuros tienen efectos durables.

Factores de riesgo para DDC incluyen nacimiento PT, sexo masculino (28), y volumen cerebral disminuido a la edad de término (25). Setanen y colegas (25) propusieron que la RNM volumétrica del cerebro a la edad de término puede proveer una herramienta para identificar infantes en riesgo de déficit neuromotor posterior. En cuanto a los resultados a largo plazo, PC es consistentemente asociada con un espectro de morbilidades neurosensoriales más severas, incluyendo desórdenes convulsivos, ceguera, y déficit auditivo (29). Además de los déficits de coordinación, incluyendo dificultades en escritura y balance, DDC puede estar asociada con desafíos académicos, problemas conductuales, y menor participación en deportes (30). A la edad escolar, DDC está asociada con scores más bajos en tests académicos y cognitivos y mayores problemas de conducta (28).

Intervenciones médicas prenatales, incluyendo esteroides antenatales (31) y sulfato de magnesio (32, 33), e intervenciones neonatales, incluyendo indometacina (34) y cafeína (35, 36), han mostrado estar asociadas con al menos una reducción parcial en las tasas de PC y DDC. Varias intervenciones motoras y educativas han mostrado alguna eficacia en reducir las manifestaciones del DDC (37-39). Se pueden tomar medidas en la UCIN para identificar infantes potencialmente en riesgo de PC o DDC, proveer apoyo de terapia física/Terapia ocupacional durante la estadía en UCIN, facilitar derivaciones a neurología para seguimiento si es necesario, proveer guías anticipatorias para padres, y referir todos los niños de alto riesgo a programas de intervención temprana al momento del egreso (40, 41).

DÉFICIT DE LENGUAJE EN PREMATUROS: ¿PUEDE HACERSE MÁS PARA MEJORAR LOS RESULTADOS?

El desarrollo temprano del lenguaje es de importancia crítica porque es el cimiento de la comunicación básica, de los procesos cognitivos, alfabetismo, e interacciones sociales. Los infantes pretérmino están en mayor riesgo de morbilidades del habla y del lenguaje, incluyendo demoras/ deficiencias en el desarrollo del vocabulario (42), procesamiento fonológico (43), comprensión del lenguaje (44), memoria verbal de corto plazo (45, 46), y desarrollo gramatical (43). Además de la injuria cerebral, factores ambientales, incluyendo raza no-blanca y etnicidad Hispana, han sido asociados con demoras tempranas del habla y el lenguaje entre infantes MPT con menos de 1000 g de PN. Los niños negros y los hispanos tienen scores de lenguaje más bajos que los blancos a los 18 a 22 meses de edad, aún después de ajustar por confundidores (47). Un estudio de la NRN reportó que los niños nacidos menores de 28 semanas de EG cuya lengua primaria fue el español tenían scores de lenguaje en Bayley más bajos pero scores cognitivos similares comparados con niños cuya lengua primaria era el inglés (48). Los investigadores sugirieron que los hallazgos pueden, en parte, ser secundarios al uso de herramientas de prueba basadas en lengua inglesa que introducen sesgo. Además, el bajo NSE es bien conocido como asociado con alteraciones del lenguaje ambiental, disminución de exposición temprana al lenguaje, y subsiguiente retraso en el lenguaje (49, 50).

Respuestas al lenguaje ambiental aparecen en la vida fetal. La cóclea del oído interno completa el desarrollo entre las 24 y 26 semanas de gestación, y la recepción auditiva se inicia durante este período. Las respuestas de parpadeo o sobresalto a estímulos vibro acústicos son obtenidas primero in el feto a las 24 a 26 semanas de EG, con respuestas consistentes para las semanas 27 a 28 de gestación (51). A las 27 semanas hasta las 29 semanas EG, el umbral auditivo in útero es aproximadamente 40 dB. El feto diferencia la voz materna de la voz de un extraño aproximadamente entre las 32 a 37 semanas de EG con cambios en la frecuencia cardíaca, sugiriendo reacción pre atención (52). Los fetos tienen la capacidad de diferenciar la voz materna de la paterna (53). Los infantes de término prefieren la voz humana a cualquier otro estímulo acústico y prefieren la voz materna a otras voces femeninas y a la voz paterna (54-57).

El infante prematuro extremo, sin embargo, abandona el ambiente protector del útero tan temprano como las 22 a 23 semanas de gestación y entra a un ambiente de lenguaje no-óptimo ruidoso y estresante de la UCIN por períodos extensos de hasta 2 a 6 meses. Los primeros 3 años de edad representan un período sensible de la plasticidad cerebral, con el ambiente sensorial impactando el crecimiento cerebral, estructuras, conectividad y función (58). La exposición del cerebro prematuro al ambiente de UCIN altera la función neuronal, que puede alterar subsiguientemente el desarrollo (59, 60). El infante de término, sin embargo, va a casa en 1 a 3 días y está expuesto al tacto, habla, sonidos, e interacciones sociales dentro de una típica unidad familiar.

Pese al ambiente subóptimo, el infante prematuro temprano comienza a responder a los estímulos auditivos hacia las 24 semanas de EG, con respuestas consistentes hacia las 28 semanas y preferencias distintivas hacia la voz materna (61). Los infantes prematuros también han mostrado responder a grabaciones de sonidos y voz materna disminuyendo su frecuencia cardíaca, lo cual ha sido interpretado como aumento de la relajación del infante (62).

¿Debería proveerse intervención de lenguaje en la UCIN? Se ha mostrado que el aumento de la exposición a la experiencia temprana de lenguaje para los niños de término en la forma de conversaciones y habla con miembros de la familia está asociada con mejor tamaño de vocabulario y CI (49, 50). El equipo de los autores investigó las vocalizaciones de los prematuros y el ambiente de lenguaje en la UCIN con registros de 16 horas de habla adulta, vocalizaciones de niños, turnos de conversación (TCs), silencio y ruido. El aparato de registro de 2 onzas puede ser ubicado dentro de un pequeño chaleco que lleve el infante o puede ubicarse inmediatamente adyacente al niño. El Análisis de Lenguaje Ambiental (LENA) con algoritmos para identificación del habla ha sido demostrado confiable, con 82% de exactitud para adultos y 76% de exactitud para infantes y niños (63). El informe de un registro típico, que se utiliza para proveer información al padre, se muestra en la Fig. 1. Está dividido en 4 dominios, incluyendo el ambiente de audio, las vocalizaciones del niño, CTs, y el número de palabras adultas habladas cada hora. El impreso se revisa con los padres, tiempos de vigilia con interacciones altas y bajas son identificados, y se pueden establecer metas para el tiempo y la intensidad de las conversaciones dirigidas al niño.

Los hallazgos del estudio revelaron que los infantes EBPN vocalizan tan temprano como a las 8 semanas antes de su fecha de término, que el habla del padre es un significativo predictor tanto de las vocalizaciones y CTs a las 32 y 36 semanas EG, y que los infantes EBPN son expuestos a significativamente más palabras de sus padres que de los cuidadores de la UCIN (64). Además, cada 100 palabras adultas de aumento en el recuento (AWC)/h en la UCIN a las 32 semanas de gestación estuvo asociado con un aumento de 2 puntos en el score compuesto de lenguaje en Bayley-III ($p=.04$) a los 18 meses. Cada aumento de 100 AWC/h a las 36 semanas de gestación estuvo asociado con un aumento de 1.2 en el score cognitivo de Bayley- III (p= .004) y un aumento de 0.3 en comunicación expresiva a los 18 meses (p= .07). Esto es altamente sugestivo de que la conversación parental en UCIN 4 y 8 semanas previas al término tiene un impacto potente en el subsiguiente lenguaje del infante y el desarrollo cognitivo (65).

Un estudio reciente (66) de niños de 3 a 6 años de edad usando registros LENA y RNM funcional identificaron que el aumento de CTs estuvo asociado con más elevada educación parental, mayor ingreso, scores compuestos verbales del niños más altos, y activación bilateral del lóbulo temporal superior en RNM. Las correlaciones entre activación durante el procesamiento del lenguaje y CTs continuaron significativas después de ajustar por educación parental, scores de los tests, AWC, y vocalizaciones del niño. En un modelo de mediación, el efecto de TCs sobre los scores de lenguaje estuvo mediado por activación del giro frontal inferior izquierdo. Los investigadores concluyeron que esta es la primera evidencia que los patrones de activación neuronal subyacen a la relación entre la exposición al lenguaje interactivo reflejada por CTs y las capacidades de lenguaje del niño (66).

Estos hallazgos apoyan fuertemente el concepto de implementar cuidado integrando a la familia (67) en la UCIN y sugieren que los infantes pretérmino se benefician con el estímulo de la presencia de sus padres y la interacción, incluyendo el cuidado, cuidado canguro, abrazo, habla, canto, y lectura. La visita abierta y las UCIN de habitación privada (68-70) con mayor compromiso de la madre y cuidado del desarrollo son beneficiosas. Las políticas que remueven barreras y fomentan la presencia parental y la participación en la UCIN son estimuladas.

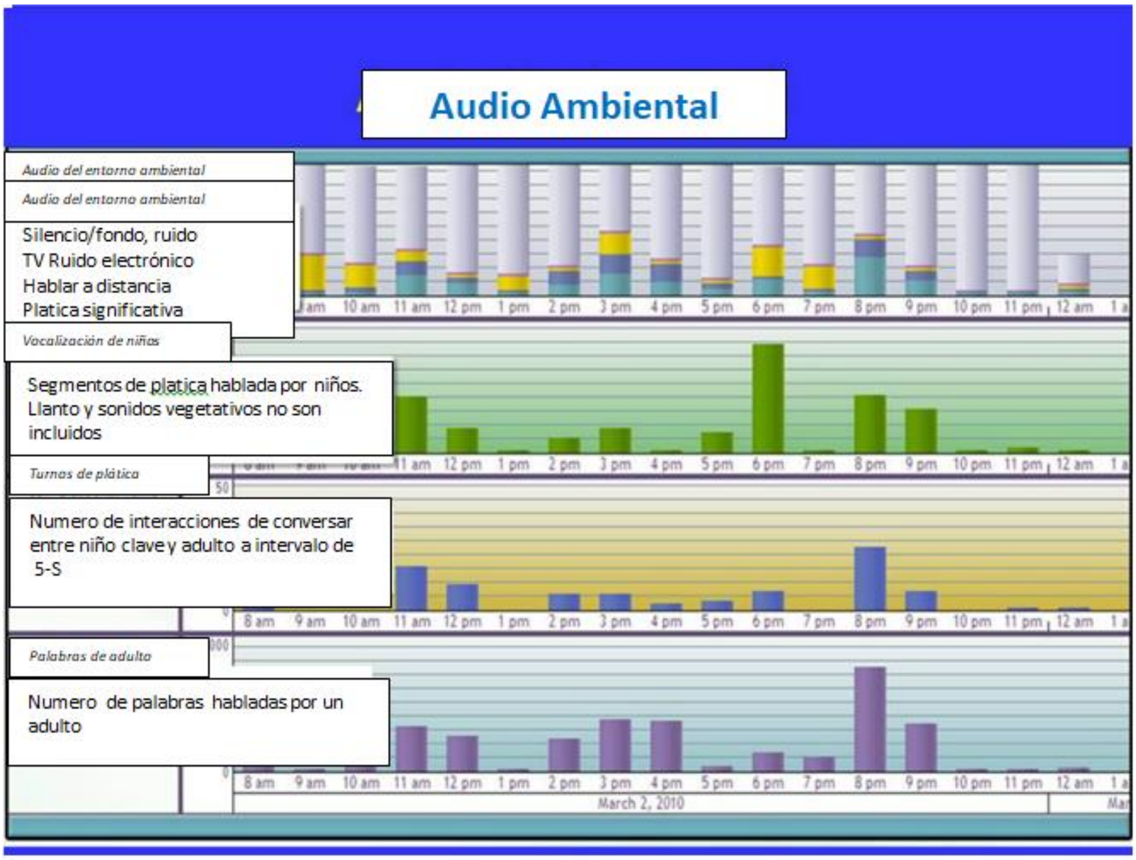

Figura 1 Producción de la grabación

RIESGOS SOCIOECONÓMICOS, NIVEL DE EDUCACIÓN MATERNO, Y MÁS ALLÁ

La salud en la infancia está estrechamente ligada a la ventaja social, y, típicamente, mejor nivel SE está asociado a resultados más óptimos (71-73). La medición de la ventaja o desventaja social es con frecuencia difícil de lograr pero puede incluir una variedad de indicadores, tales como nivel de educación, nivel de ingreso, ocupación y seguro de salud. En la población prematura, hay evidencia que tanto el bajo nivel SE y variables biológicas específicas son factores de riesgo para pobres resultados de desarrollo (74-78). En la medida en que se está comenzando a explorar la influencia de estos riesgos a largo plazo, particularmente en la era post-surfactante, interacciones complejas entre estos factores se están haciendo evidentes.

Estudios actuales que examinan los efectos del nivel SE continúan resaltando la importante influencia del estado educativo sobre los resultados del neurodesarrollo. Linsell y colegas (79), en una revisión sistemática, mostraron que la baja educación parental y la raza no blanca/etnicidad fueron predictores de déficits globales pre-escolares (antes de la edad escolar, específicamente 1.5-2.5 años de edad) en infantes MPT. Asztalos y colegas (80), de la Red de Seguimiento Canadiense, reportaron asociación positiva de los resultados del desarrollo entre los 18-21 meses con el nivel de educación materna. Para niños nacidos antes de las 29 semanas de EG, los scores cognitivo y de lenguaje mejoraron en la medida que aumentaba la educación del cuidador, y los scores se acercaron a los valores medios de 100 sólo en infantes de madres con los más altos niveles de educación.

El impacto del nivel de educación parental parece persistir hasta los primeros años de escuela, particularmente sobre los resultados cognitivos y conductuales. En una cohorte de infantes prematuros menores de 28 semanas de gestación sin morbilidades, tales como PC, ceguera, o sordera, el CI del niño estuvo positivamente asociado con la educación materna más alta (81). En la cohorte EPIPAGE, Beaino y colegas (74) definieron nivel SE como el nivel de educación materno y paterno. La baja educación paterna fue el principal predictor para retraso cognitivo leve (OR ajustado 3.43; IC 2.01-5.83) y un significativo predictor para retraso cognitivo severo (OR 2.6; IC 95%, 1.29-5.24) a los 5 años de edad, junto al ser PEG y LPV (74). Potharst y colegas (82) reportaron acerca de los resultados a los 5 años para niños <30 sem de EG, y, comparados con controles de término, la diferencia media de CI pretérmino-término fue 5 puntos, si la educación parental era alta, y aumentaba a 15 puntos, si la educación parental era baja. Patrones similares se vieron en el comportamiento. El CI materno, ingresos, ocupación, y hogar monoparental sea en forma independiente o como co-variables muestran similares asociaciones con los resultados cognitivos y de conducta (83-86).

A medida que más cohortes de niños prematuros son seguidas longitudinalmente, los investigadores ahora pueden evaluar la contribución a largo plazo de las influencias sociales. Joseph y colegas (87) reportaron que los niños de madres con educación en el nivel más bajo en la cohorte ELGAN tuvieron más posibilidad de puntuar igual o más de 2 DS debajo de la media en una batería de tests neurocognitivos a la edad de 10 años. Los riesgos del nivel SE desfavorable, particularmente si asociados a daño cerebral, también han sido explorados. En una cohorte europea de 200 infantes EBPN nacidos entre 1993 y 1998, la baja educación materna fue el factor de riesgo más significativo para CI disminuido; sin embargo, HIV grado III/IV o LPV continuaron impactando negativamente a los 13 años de edad (88). Para este estudio, las trayectorias del desarrollo de niños con madres con mejor nivel versus más bajo nivel de educación fueron diferentes independientemente de la injuria cerebral. Los niños de madres con más alta educación tuvieron incrementos en los scores compuestos de CI entre los 6 y 13 años, mientras aquellos con más baja educación materna permanecieron esencialmente sin cambios. Una cohorte australiana de la misma era de estudio, abarcando PT tempranos /EPT y controles con PN normal (89), reportaron una fuerte y persistente influencia de la HIV en la cognición y desempeño académico a los 2, 5, 8, y 18 años de edad. La educación materna y la clase social, sin embargo, no alcanzaron significancia estadística hasta los 8 años y más.

La interpretación de los efectos de las variables socioeconómicas sobre los resultados a largo plazo es un desafío. Muchas situaciones sociales adversas están inter-relacionadas, tienden a agruparse, y tienen relaciones dosis-respuesta con la poca salud (90, 91). La salud mental positiva es delineada por varios aspectos socioeconómicos y físicos y es un componente integral de relaciones enriquecidas, particularmente para la díada madre-hijo. La depresión materna, ansiedad, y estrés han sido asociadas con baja auto eficacia materna, definida como la percepción de la madre de su capacidad parental (92, 93). Al egreso de UCIN, las madres con historia de alteraciones de salud mental reportan disminución de la confianza en sí mismas comparadas con madres sin historia de antecedentes de desórdenes mentales (94). Hawes y colegas (95) reportaron que la presteza disminuida para el alta de UCIN está asociada con síntomas depresivos postalta. Importante, dentro del primer año de edad, la depresión materna y la ansiedad han sido vinculadas a desregulación del infante, temperamento difícil, y alteraciones del sueño así como a interacciones parental-infante comprometidas e inadecuadas prácticas de cuidado parental (96-99).

Se ha publicado menos sobre los efectos a largo plazo de la depresión materna y ansiedad en los resultados de infantes prematuros; los resultados con frecuencia son conflictivos y representan diferentes patrones de síntomas (100-102). Una cohorte prospectiva de infantes MBPN nacidos en Finlandia fue seguida desde la infancia hasta la edad escolar, y, después de ajustar por nivel de educación materna, se reportaron asociaciones significativas de síntomas de depresión y estrés parental con problemas cognitivos, conductuales y socioemocionales en el niño entre los 2 a 5 años de edad (103-105). Se ha sugerido que con el tiempo, los padres de niños vulnerables aumentan sus niveles de estrés. Singer y colegas (106) reportaron que las madres de infantes MBPN de alto riesgo percibían aumento del estrés desde la infancia temprana hasta la adolescencia comparadas con madres de niños e término o bajo riesgo.

Es importante reconocer que estos estudios a largo plazo no pueden determinar mecanismos causales, porque las asociaciones entre el bienestar psicológico parental i la salud/desarrollo del niño son multifactoriales y bidireccionales. Mediadores de estrés materno, depresión, y ansiedad, sin embargo, incluyen BPN, baja educación materna, dificultades en el comportamiento del infante y el niño, carencia de apoyo social para la familia, y pobre salud del niño (100, 106-109). Adicionalmente, el campo emergente de la epigenética está comenzando a descubrir efectos de eventos adversos tempranos en el infante en desarrollo. Un mecanismo en particular, la metilación del ADN de genes que codifican los reguladores del estrés del eje hipotálamo-pituitario- adrenal, es prometedor (110). En la población prematura, conexiones entre la ansiedad y depresión maternas y alteración en los genes relacionados al estrés del infante han sido reportados, resaltando otro mecanismo más influenciando los resultados del desarrollo (111-113).

En conclusión, las investigaciones apuntando a los riesgos socioeconómicos proveen oportunidades para mejorar los resultados en el infante pretérmino vulnerable. La evidencia sugiere que las intervenciones tempranas, en particular aquéllas que enfocan en fortalecer las relaciones parental-niño, tienen una influencia positiva sobre los resultados motor, cognitivo, y de conducta y pueden disminuir los síntomas parentales de depresión y ansiedad (38, 114-116). La importancia de apoyar la salud mental parental es ahora ampliamente reconocida, y las recomendaciones estimulan a comenzar en la UCIN (117). La exploración continuada de las complejas interacciones de las contribuciones psicológicas, social, y médicas es necesaria así como hacer esfuerzos para identificar estrategias efectivas que optimicen los resultados a largo plazo para los infantes prematuros y sus familias.

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Neurodevelopmental Follow-up of Preterm Infants

What Is New?

Elisabeth C. McGowan, MD[a,b], Betty R. Vohr, MD[a,b,*]

KEYWORDS

- Neurodevelopment • Cerebral palsy • Premature infants
- Developmental coordination disorder • Language • Socioeconomic status

KEY POINTS

- Although the rate of severe cerebral palsy (CP) has decreased among preterm infants, the rate of mild CP and the identification of developmental coordination disorder (DCD) have increased in this population.
- DCD has been shown to have effects persisting throughout school age and adolescence.
- There is increasing recognition of the importance of early interactive language exposure on the language development of infants.
- Although maternal education level continues to be the most frequently reported socioeconomic status indicator, there is increasing evidence of the impact of psycho-socioeconomic adversities on preterm neurodevelopmental and behavioral outcomes.
- Identification of adverse maternal mental health in the neonatal ICU and postdischarge provides an opportunity for intervention in former preterm infants and their mothers.

There is increasing evidence of ongoing changes occurring in short-term and long-term motor and language outcomes in the preterm population. In addition, there is increased awareness of the negative impact of family psycho-socioeconomic adversities on preterm outcomes. This review provides updates on 3 areas of reported change in neurodevelopmental follow-up and outcomes in preterm infants: motor impairments, language delays and disorders, and the impact of family psycho-socioeconomic adversities on outcomes.

MOTOR IMPAIRMENTS AMONG PRETERM INFANTS—A CHANGING PICTURE

Modern neonatal intensive care has contributed to increased survival of infants at the limits of prematurity,[1–4] and changes in the rates of neonatal morbidities[5] and

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[a] Department of Pediatrics, Alpert Medical School of Brown University, Women & Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905-2499, USA; [b] Department of Pediatrics, Alpert Medical School of Brown University, Neonatal-Follow-up Clinic, Women & Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905-2499, USA
* Corresponding author. 101 Dudley Street, Providence, RI 02905-2499.
E-mail address: bvohr@wihri.org

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neurodevelopmental impairments.[1,3] A key component of neurodevelopmental impairment is cerebral palsy (CP).[6] During the early years of neonatology, a primary focus of follow-up studies was on identification of rates of CP.[7–9] CP is often associated with other long-term sequelae, including cognitive, sensory, and language impairments; seizure disorders; and growth abnormalities. Confirmation of this diagnosis is difficult to achieve before 18 months to 24 months of age, especially if the manifestation is mild. Categorization of degree of CP severity based on the Gross Motor Function Classification System[10] into mild (level 1), moderate (levels 2 and 3), and severe to profound (levels 4 and 5) is well accepted.

Recent studies suggest changes in both the rates of CP and the degree of severity.[5,11–14] The Neonatal Research Network study of extreme preterm infants less than or equal to 27 weeks' gestation born from 2011 to 2014 and evaluated at 18 months to 26 months of age showed that the rate of CP decreased during this time period from 16% to 12%.[5] In addition, whereas the rate of severe CP decreased by 43%, the rate of mild CP increased by 13% during the study period. An additional 19% of children had a suspect neurologic examination. This indicates that improvement of motor outcomes is occurring in conjunction with the increased survival of the most preterm neonates. This finding supports that just as there is a spectrum of white matter abnormalities among preterm infants, there is a spectrum or continuum of motor findings ranging from mild to profound.[15,16]

Former preterm infants are at risk of a range of motor abnormalities, including delayed motor milestones, balance abnormalities, challenges with manual dexterity, and generalized coordination abnormalities now codified as developmental coordination disorder (DCD) with the Movement Assessment Battery for Children (MABC)–Second Edition (MABC-2).[17–19] The American Psychiatric Association in 2013 defined DCD as impairment in coordinated motor skills that significantly interfere with performance in everyday activities. Abilities assessed include manual dexterity, aiming, and catching and balance. Scores above the 15th percentile are considered normal, scores in the 6th to 15th percentiles are at risk, and scores in less than or equal to the 5th percentile are consistent with significant motor difficulty. Although motor delays are evident in early childhood, the diagnosis of DCD is often not made until school age.[20] A series of studies reporting DCD at ages 3 years to 24 years is shown in **Table 1**.

Kwok and colleagues[21] examined the predictive value of the MABC-2 at 3 years to predict DCD at 4.5 years among very preterm (VPT) children, defined by the investigators as 24 weeks' to 32 weeks' gestation, and reported a sensitivity of 90% and specificity of 69%, indicating many false-positive results. The investigators concluded that at this early age, the MABC is highly sensitive but with limited specificity in identifying VPT children who are at risk of DCD. The Griffiths and colleagues' study[22] reported that 25% of infants born at less than 30 weeks' gestation had scores consistent with significant motor difficulty ($\leq$5%) at both 4 years of age and 8 years of age, and the MABC-2 at 4 years had high sensitivity (79%) and specificity (93%) for predicting motor impairment at 8 years. Bolk and collegues[23] examined a large cohort of apparently healthy extreme preterm infants (defined as 22–26 weeks' gestation) compared with term controls at 6.5 years of age and reported the highest rate of DCD of 37.1% in preterm infants versus 5.5% in term infants. Three studies from the Victorian Infant Collaborative Study Group[24] of infants born at 22 weeks' to 27 weeks' gestation identified consistently low but increasing rates of DCD during 3 time periods between 1991 and 2005, with increasing rates of 2%, 8%, and 7%. The findings are similar to those of Setanen and colleagues[25] in a Finish cohort at 11 years of age. Finally, a study[26] from Norway reported rates of DCD of 29% in a

Table 1
Developmental coordination disorder

Authors, Year Published	Gestational Age	Date of Birth or Visits	Sample Size	Age of Assessment	Movement Assessment Battery for Children Coordination Disorder	
Kwok et al,[21] 2018 Canada	24–32 wk	Visits 2010–2015	165	3 y 4.5 y	Prediction Sensitivity 90% Specificity 69%	
Griffiths et al,[22] 2017 Australia	<30 wk	2005–2007	96	4 y 8 y	<5th% 25th% 25th%	
Bolk et al,[23] 2018 Sweden	22–26 wk	Birth 2004–2007	229 preterm 244 term	6.5 y	<5th% Preterm Term	 37.1% 5.5%
Davis et al,[28] 2007 Australia; Victorian Infant Collaborative Study Group	22–27 wk	Birth 1991–1992	163	8 y	<15th% <5th%	10% 2%
Roberts,[27] 2011 Australia; Victorian Infant Collaborative Study Group	22–27 wk	1997	132 154 term	8 y	EP <15th% EP <5th % T <5th%	23% 16% 5%
Spittle et al,[24] 2018 Australia: Victorian Infant Collaborative Study Group	22–27 wk	1991–2005	Study Year 1991–1992 226 1997 172 2005 189	8 y	<5th% <5th% <5th%	2% 8% 7%
Setanen et al,[25] 2016 PIPARI Study Group Finland	23–35 wk	2001–2004	82	11 y	<5th%	8%
Husby et al,[26] 2013 Norway	VLBW <1500 g	1986–88	36 VLBW 37 term	14 y 23 y	<5th% <5th%	29% 29%

small cohort of former very-low-birthweight (VLBW) infants, less than 1500 g, born from 1986 to 1988 at both ages 14 years and 23 years. At 23 years, the VLBW subjects had poorer total motor scores and subscores for manual dexterity and balance compared with the term comparison group. After exclusion of the 4 VLBW subjects with CP, however, the difference in total MABC-2 score between study groups was no longer significant.[26] This study has a small sample size and the results need to be replicated in larger studies. The percentage identified in reports are impacted if children with CP are excluded.[27] The findings overall suggest that early motor coordination challenges among former preterm infants have lasting effects.

Risk factors of DCD include preterm birth, male gender,[28] and decreased brain volume at term age.[25] Setanen and colleagues[25] propose that volumetric brain MRI at term age may provide a tool to identify infants at risk for later neuromotor impairment. Relative to longer-term outcomes, CP is fairly consistently associated with a spectrum of more severe neurosensory morbidities, including seizure disorders, blindness, and hearing impairment.[29] In addition to coordination deficits, including difficulties writing and balancing, DCD can be associated with academic challenges, behavior problems, and decreased participation in sports.[30] At school age, DCD is associated with lower cognitive and academic test scores and greater behavior problems.[28]

Prenatal medical interventions, including antenatal steroids[31] and magnesium sulfate,[32,33] and neonatal interventions, including indomethacin[34] and caffeine,[35,36] have been shown associated with at least partial reduction in rates of CP and DCD. Several motor and education-based interventions have shown some efficacy in reducing the manifestations coordination disorder.[37–39] Steps can be taken in the neonatal ICU (NICU) to identify infants potentially at risk of CP or DCD, provide physical therapy/occupational therapy support during the NICU stay, facilitate referrals to neurology for follow-up as needed, provide anticipatory guidance for parents, and refer all high-risk infants to early intervention programs at the time of discharge.[40,41]

PRETERM LANGUAGE IMPAIRMENTS: CAN MORE BE DONE TO IMPROVE OUTCOMES?

Early development of language is critically important because it is the building block for basic communication, cognitive processes, literacy, and social interactions. Preterm infants are at increased risk of speech and language morbidities, including mild to moderate delays/deficiencies in vocabulary development,[42] phonological processing,[43] language comprehension,[44] verbal short-term memory,[45,46] and grammatical development.[43] In addition to brain injury, environmental factors, including both nonwhite race and Hispanic ethnicity, have been associated with early speech and language delays among VPT infants with less than 1000-g birthweight. Black and Hispanic toddlers had lower language scores than whites at 18 months to 22 months, even after adjustment for confounders.[47] A Neonatal Research Network study reported that children born at less than 28 weeks' gestation whose primary language was Spanish had lower Bayley Scales of Infant and Toddler Development (BSID) language scores but similar cognitive scores compared with children whose primary language was English.[48] The investigators suggested the findings may, in part, be secondary to use of English language–based testing tools that introduce bias. In addition, low socioeconomic status (SES) is well known to be associated with alterations in the language environment, decreased early language exposure, and subsequent language delay.[49,50]

Responses to the language environment begin in fetal life. The cochlea of the inner ear completes development between 24 weeks' and 26 weeks' gestation, and auditory reception starts during this time period. Blink-startle responses to vibroacoustic stimuli are first elicited in the fetus at 24 weeks' to 26 weeks' gestation, with consistent responses by 27 weeks' to 28 weeks' gestation.[51] At 27 weeks' to 29 weeks' gestation, the hearing threshold in utero is approximately 40 dB. The fetus differentiates the maternal voice from a stranger's voice at approximately 32 weeks' to 37 weeks' gestation by changes in heart rate, suggesting a preattention reaction.[52] Fetuses have the ability to differentiate a maternal voice from a paternal voice.[53] Term infants prefer human voice to other acoustic stimuli and prefer a maternal voice to other female voices and to a paternal voice.[54–57]

The extreme preterm infant, however, leaves the protective sound environment of the uterus as early as 22 weeks' to 23 weeks' gestation and enters the noisy and stressful NICU nonoptimal language environment for extended periods of up to 2 months to 6 months. The first 3 years of age represent a sensitive period of brain plasticity, with the sensory environment impacting brain growth, structures, connectivity, and function.[58] Exposure of the preterm brain to the NICU environment alters neuronal differentiation, which may alter subsequent development.[59,60] The term infant, however, goes home in 1 day to 3 days and is exposed to the touch, talk, sounds, and social interactions within a typical family unit.

Despite the nonoptimal environment, the early preterm infant begins to respond to auditory stimuli by 24 weeks' gestation, with consistent responses by 28 weeks and distinct preferences shown for maternal voice.[61] Preterm infants have also been shown to respond to recordings of maternal sounds and voice by lowering their heart rate, which has been interpreted as increased infant relaxation.[62]

Should language intervention be provided in the NICU? It has been shown that increased exposure to early language experience for term children in the form of conversations and talk with family members is associated with improved child vocabulary size and IQ.[49,50] The authors' team investigated preterm vocalizations and the language environment of the NICU with 16-hour audio recordings of adult speech, child vocalizations, conversation turns (CTs), silence, and noise. The 2-oz recording device can be placed into a small vest the infant wears or can be placed immediately adjacent to the infant. Language Environment Analysis (LENA) speech-identification algorithms have been determined to be reliable, with 82% accuracy for adults and 76% accuracy for infants and children.[63] Output of a typical recording, which is used to provide feedback to the parent, is shown in **Fig. 1**. It is divided into 4 domains, including the audio environment, child vocalizations, CTs, and number of adult words spoken each hour. The printout is reviewed with the parents, awake times with high and low interactions are identified, and goals can be set for timing and intensity of child-directed conversations.

Study findings revealed that extremely-low-birthweight (ELBW) infants vocalize as early as 8 weeks before their due date, that parent talk is a significant predictor of both infant vocalizations and CTs at 32 weeks' and 36 weeks' gestation, and that ELBW infants are exposed to significantly more words from their parents than from NICU caretakers.[64] In addition, every increase in 100 adult word count (AWC)/h in the NICU at 32 weeks' gestation was associated with a 2-point increase in the BSID, Third Edition, language composite score ($P = .04$) at 18 months. Every increase in 100 AWC/h at 36 weeks' gestation was associated with a 1.2-point increase in BSID, Third Edition, cognitive composite score ($P = .004$) and a 0.3-point increase in expressive communication at 18 months ($P = .07$). This is highly suggestive that parent talk in the NICU 4 weeks and 8 weeks prior to an infant's due date has a powerful impact on subsequent infant language and cognitive development.[65]

A recent study[66] of term 3-year-old to 6-year-old children using LENA recordings and functional MRI identified that increased CTs were associated with higher parent education, higher income, higher child composite verbal scores, and bilateral MRI superior temporal lobe activation. Correlations between activation during language processing and CTs remained significant after adjustment for parent education, test scores, AWC, and child vocalizations. In a mediation model, the effect of CTs on language scores was mediated by activation of the left inferior frontal gyrus. The investigators concluded that this is the first evidence that neural activation patterns underlay

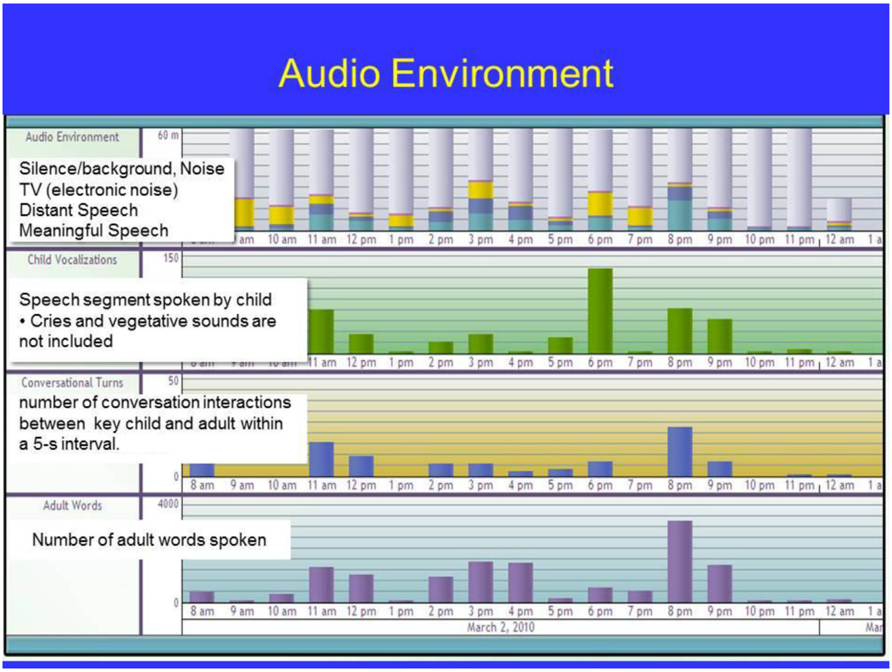

Fig. 1. Recording output.

the relationship between interactive language exposure reflected by CTs and child language abilities.[66]

These findings strongly support the concept of implementing family-integrated care[67] in the NICU and suggest that preterm infants benefit from enhanced parent presence and interaction, including caretaking, kangaroo care, cuddling, talking, singing, and reading. Open visiting and the single-room NICUs[68–70] with enhanced maternal involvement and developmental care are beneficial. Policies that remove barriers and encourage parent presence and participation in the NICU are encouraged.

SOCIOECONOMIC RISKS, MATERNAL EDUCATION LEVEL, AND BEYOND

Childhood health is closely linked to social advantage, and, typically, improvement in SES is associated with more optimal outcomes.[71–73] Measurement of social advantage or disadvantage is often difficult to capture but may include a variety of indicators, such as education status, income level, occupation, and insurance status. In the preterm population, there is evidence that both low SES and specific biologic variables are risk factors for poor developmental outcomes.[74–78] As the long-term influence of these risks is beginning to be explored, particularly in the post-surfactant era, complex interactions among these factors are becoming evident.

Current studies examining the effects of SES continue to highlight the important influence of educational status on neurodevelopmental outcomes. Linsell and colleagues,[79] in a systematic review, showed that low parental education and nonwhite race/ethnicity were predictors of pre-school (before school age, specifically 1.5 – 2.5 years of age) global impairments in VPT infants. Asztalos and colleagues,[80] of the Canadian Neonatal Follow-Up Network, reported positive association of 18-month to 21-month developmental outcomes with maternal education level. For infants born at less than 29 weeks' gestation, cognitive and language scores improved as caregiver education increased, and scores approached mean values of 100 only for infants of mothers with the highest levels of education.

The impact of parent education level seems to persist into early school years, particularly on cognitive and behavior outcomes. In a cohort of preterm infants less than 28 weeks' gestation without morbidities, such as CP, blindness, or deafness, child IQ was positively associated with higher maternal education.[81] In the EPIPAGE cohort, Beaino and colleagues[74] defined SES as both maternal and paternal education status. Low parental education was the main predictor for mild cognitive delay (adjusted odds ratio [OR] 3.43; 95% CI, 2.01–5.83) and a significant predictor for severe cognitive delay (OR 2.6; 95% CI, 1.29–5.24) at 5 years of age, along with small-for-gestational-age status and cystic periventricular leukomalacia.[74] Potharst and colleagues[82] reported on 5-year outcomes for infants less than 30 weeks' gestation, and, compared with term controls, the preterm-term mean IQ difference was 5 points, if parent education was high, and increased to 15 points, if parent education was low. Similar patterns were seen for behavior. Maternal IQ, income, occupation, and single-parent household as either independent or composite variables show similar associations with cognitive and behavior outcomes.[83–86]

As more preterm cohorts are followed longitudinally, investigators are now able to evaluate the longer-term contribution of social influences. Joseph and colleagues[87] reported that children of mothers in the lowest education stratum in the ELGAN cohort were more likely to score greater than or equal to 2 SDs below the mean on a battery of neurocognitive tests at 10 years of age. The risks of unfavorable SES, particularly in association with brain injury, have also been explored. In a European cohort of 200 ELBW infants born between 1993 and 1998, low maternal education was the most significant risk factor for decreased IQ; however, grade III/IV intraventricular hemorrhage or periventricular leukomalacia continued to have a negative impact at 13 years of age.[88] For this study, the developmental trajectories for children of mothers with higher versus lower education were different irrespective of brain injury. Children of mothers with the highest education had increases in composite IQ scores between 6 years and 13 years of age, whereas those with lower maternal education remained essentially unchanged. An Australian cohort from the same study era, comprising both early preterm/ELBW infants and normal birthweight controls,[89] reported a strong and persistent influence of intraventricular hemorrhage on cognition and academic performance at 2 years, 5 years, 8 years, and 18 years of age. Maternal education and social class, however, did not reach statistical significance until years 8 and beyond.

The interpretation of the effects of socioeconomic variables on long-term outcomes is challenging. Many adverse social situations are inter-related, tend to cluster, and have dose-response relationships with poor health.[90,91] Positive mental health is shaped by various socioeconomic and physical environments and is an integral component of enriched relationships, particularly for the mother-infant dyad. Maternal depression, anxiety, and stress have been associated with low maternal self-efficacy, defined as a mother's belief in her ability to parent.[92,93] At NICU discharge, mothers with a history of mental health disorders report decreased self-confidence compared with mothers without a history of mental health disorders.[94] Hawes and colleagues[95] report that decreased NICU discharge readiness is associated with postdischarge depressive symptoms. Importantly, within the first year of age, maternal depression and anxiety have been linked to infant dysregulation, difficult temperament, and sleep disturbances as well as compromised parent-infant interactions and inadequate parental caregiving practices.[96–99]

Less has been published on the long-term effects of maternal depression and anxiety on preterm infant outcomes; results are often conflicting and portray different patterns of symptoms.[100–102] A prospective cohort of VLBW infants born in Finland was followed from infancy to school age, and, after adjustment for maternal education level, significant associations of parental depression and stress symptoms with child cognitive, behavior, and socioemotional problems were reported between 2 years to 5 years of age.[103–105] It has been suggested that over time, parents of vulnerable infants experience increasing levels of stress. Singer and colleagues[106] reported that mothers of high-risk VLBW infants perceived increased stress extending from early childhood through adolescence compared with mothers of term or low-risk VLBW children.

It is important to recognize these long-term studies cannot determine causal pathways, because associations between parent psychological wellness and infant health/development are multifactorial and bidirectional. Mediators of maternal stress, depression, and anxiety, however, include low birthweight, low maternal education, infant and child behavior difficulties, lack of family social supports, and poor child health, all of which are more prevalent in the preterm population.[100,106–109] Additionally, the emerging field of epigenetics is beginning to uncover the effects of early adverse advents on the developing infant. One mechanism in particular, DNA methylation of genes encoding for stress regulators of the hypothalamus-pituitary-adrenal axis, shows promise.[110] In the preterm population, links between maternal anxiety and depression and alteration of infant stress-related genes have been reported, highlighting yet another pathway influencing developmental outcomes.[111–113]

In conclusion, investigations targeting psycho-socioeconomic risks provide opportunities for improving outcomes of the vulnerable preterm infant. Evidence suggests that early interventions, in particular those that focus on strengthening parent-infant relationships, have a positive influence on motor, cognitive, and behavior outcomes and may decrease parental symptoms of depression and anxiety.[38,114–116] The importance of supporting parental mental health is now widely recognized, and guidelines encourage starting this in the NICU.[117] Continued exploration of the complex interactions of psychological, social, and medical contributions is needed as efforts are made to identify effective strategies that optimize long-term outcomes for preterm infants and their families.

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