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REVIEW ARTICLE

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Omics approaches: interactions at the maternal–fetal interface and origins of child health and disease

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Immunoperinatology is an emerging field. Transdisciplinary efforts by physicians, physician-scientists, basic science researchers, and computational biologists have made substantial advancements by identifying unique immunologic signatures of specific diseases, discovering innovative preventative or treatment strategies, and establishing foundations for individualized neonatal intensive care of the most vulnerable neonates. In this review, we summarize the immunobiology and immunopathology of pregnancy, highlight omics approaches to study the maternal–fetal interface, and their contributions to pregnancy health. We examined the importance of transdisciplinary, multiomic (such as genomics, transcriptomics, proteomics, metabolomics, and immunomics) and machine-learning strategies in unraveling the mechanisms of adverse pregnancy, neonatal, and childhood outcomes and how they can guide the development of novel therapies to improve maternal and neonatal health.

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IMPACT:

- Discuss immunoperinatology research from the lens of omics and machine-learning approaches.
- Identify opportunities for omics-based approaches to delineate infection/inflammation-associated maternal, neonatal, and later life adverse outcomes (e.g., histologic chorioamnionitis [HCA]).

INTRODUCTION

Inflammation, either sterile or non-sterile, may result in preterm labor (PTL) or preterm premature rupture of membranes (PPROM).[1] Ensuing preterm birth accompanied by postnatal inflammation (a second inflammatory hit) as a result of postnatal infectious agents, hypoxia, hyperoxia, intrauterine growth restriction (IUGR), malnutrition, and/or medications may further exacerbate neonatal morbidities.[1] Preterm birth significantly impacts the infants, families, and society at large. Thus, it is imperative that novel tools to predict the development of devastating neonatal morbidities be designed, which utilize all available clinical, laboratory, and omics data as well as machine-learning (and artificial intelligence [AI]) approaches with the aim of individualizing medical therapies.

Dynamic regulation of local placental, maternal peripheral immune responses, inflammatory and anti-inflammatory cells, cytokines and signaling pathways are important contributors to maternal–fetal homeostasis.[2,3] Maternal–fetal homeostasis can be perturbed by prenatal factors such as environmental exposures, inflammation and infection, poor nutrition, and chronic maternal stress.[4] Additionally, the balance between inherent susceptibilities and resilience of the mother and fetus, gestational age (GA), birth weight (BW) at delivery, the postnatal environment, neonatal intensive care unit (NICU) course, and disease burden are important contributors to neonatal and later life outcomes. Immune system reprogramming can also be considered a core component of the developmental origins of health and disease (Fig. 1). Based on *fetal programming*, influences that occur in fetal life may persist beyond the acute stage, some may remain silent during the early postnatal life but result in lifelong morbidities.[5–7] This is especially important for preterm neonates where sustained inflammation could alter postnatal organ development and contribute to inflammation-associated neonatal morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL).[1]

The *exposome* is a term coined by Wild et al. in 2005 to describe that a phenotype is a function of the genome and environment, where the environment is all encompassing from prenatal, antenatal, and postnatal life.[8] Interactions between the exposome and genome are central for the development of chronic diseases[8] and also implicated as a cause of preterm birth.[9] Thus, reprogramming in fetal life may determine lifelong health and individual resilience or susceptibilities to disease as a function of altered early homeostasis and gene–environment balance.[7,10] In 2014, Rappaport et al. explored the role of the exposome in disease causality.[11] Although they did not target the neonatal exposome specifically, they highlighted that targeting just one investigative approach was insufficient to understand causality.[11] For instance, data weighted by epidemiological risk factors generated different risk maps for chronic disease causality when compared with data weighted by metabolic pathways.[11] Therefore, to predict disease susceptibilities,

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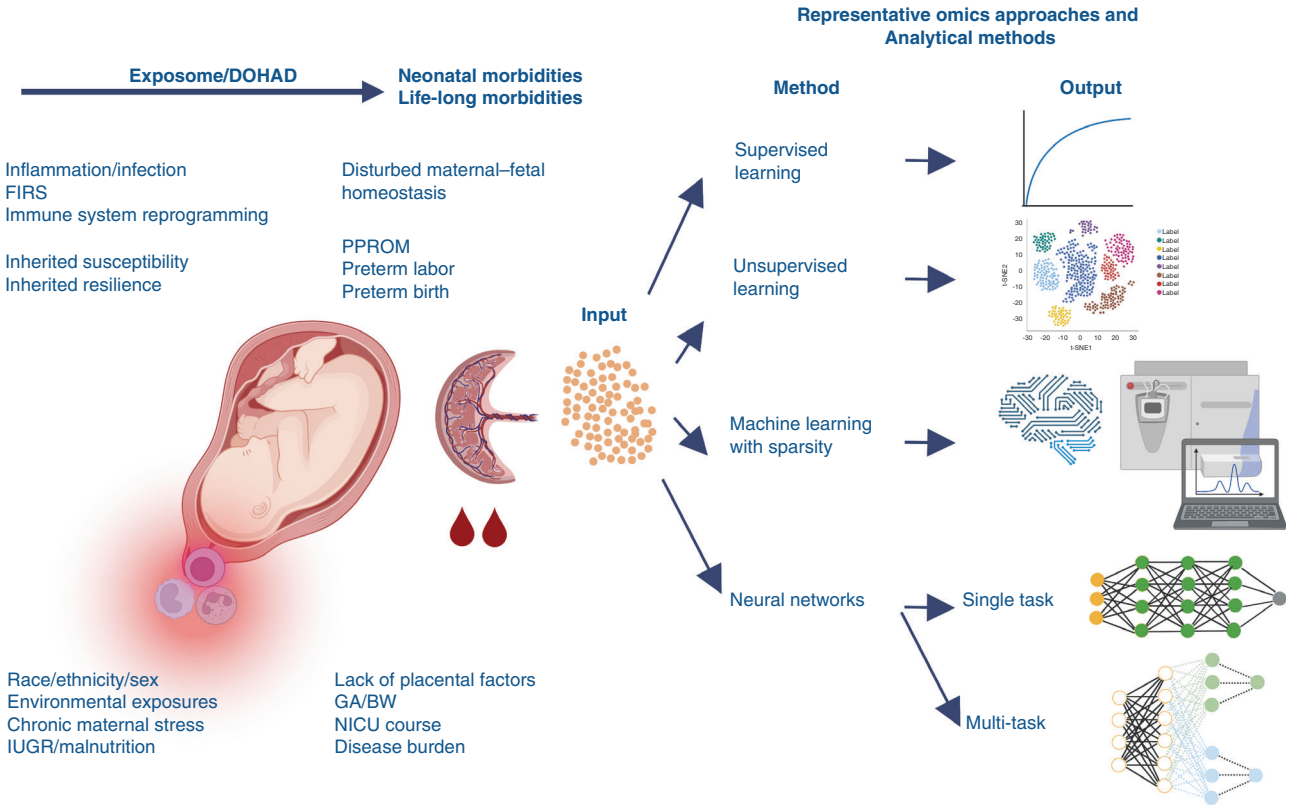

Fig. 1 Exposome, fetal programming, and representative omics approaches (immunomics, transcriptomics, metabolomics) and analytical methods (supervised, unsupervised machine-learning and neural networks) are illustrated. However, these are not mutually exclusive (for example, sparse methods are supervised; also supervised methods can be single task or multitask).

severities, and/or short- or long-term outcomes from any biological data, the complexity of the exposome must be included in any prediction algorithm.

It has been difficult to differentiate associations from causality for most neonatal morbidities. High-throughput technologies such as omics approaches allow for a comprehensive study of biologic molecules through the integration of a wide array of datasets arising from studies of the genome, transcriptome, proteome, metabolome, immunome, and microbiome.[12] Indeed, they may reveal new insights into the causative pathways of any complex disease process.[12] Generated datasets can be useful as prediction tools for common neonatal morbidities, and can help stratify patients based on their risk categories to conventional or novel therapies. Here, we provide an overview of emerging omics and machine-learning approaches to study normal and pathological pregnancies as well as some of the common neonatal morbidities that challenge clinicians working daily in the NICU.

DETERMINATION OF A HEALTHY MATERNAL–FETAL INTERFACE: MATERNAL BLOOD, PLACENTA, AND OMICS INTEGRATION

Adaptive maternal immunologic changes support the concept of its effects on immune tolerance on the developing fetus, while disruption of this homeostasis may be associated with pathological pregnancies and neonatal sequelae.[2,3,13,14] Implantation and maintenance of a healthy pregnancy and delivery corresponds with dynamic changes in NF-KB regulation during gestation.[15–17] Implantation, primarily a pro-inflammatory process, is followed by a relative uterine quiescence maintained by a negative regulation of NF-KB until induction of spontaneous labor at term. Th1, natural killer (NK) cells, macrophages, and dendritic cells (DCs) are activated during implantation.[16] Peripheral blood monocytes and T cell NF-KB downregulation contributes to healthy maternal–fetal tolerance.[15,18–20] PTL however may ensue with a dysregulation in anti-inflammatory (IL-10, Galectin-1)/pro-inflammatory (TNF-α, IL-6, IL-8, IFN-γ, MMP, COX-2) signaling.[15,21] In a genome-wide transcriptional profiling study using third trimester maternal dried bloodspots, preterm birth was found to be associated with increased NF-KB and transcripts originating from monocytes.[22] Other pregnancy pathologies such as spontaneous abortion and IUGR can occur due to an overactivation of NF-KB or alterations of normal Th1/Th17 dynamics[15,23] (Fig. 2).

Machine-learning and AI algorithms applied to high-throughput omics data have enabled recent advances in the understanding of a healthy maternal–fetal interface as well as of pathological pregnancies.[2,24–32] Novel approaches have been applied to define an *immune clock* of pregnancy, where T cell function during a healthy term pregnancy is modulated by a unique signaling pathway, namely, interleukin-2 (IL-2)-dependent signal transducer and activator of transcription-5 (STAT5ab) in naive $CD4^+$ T cells.[24] A state-of-the-art cell signaling-based elastic net (csEN) algorithm was designed to interrogate maternal whole blood immune cells prospectively collected during early, mid, and late pregnancy and accurately predicted dynamic immune alterations that were highly regulated during the course of a healthy term pregnancy.[24] Specifically, there was a progressive increase in endogenous STAT5ab signaling in memory $CD4^+$, naive $CD8^+$, memory $CD8^+$, $TCR\gamma\delta^+$ T, and $CD25^+$ $FoxP3^+$ regulatory T cells (Tregs), and endogenous STAT5ab signaling in naive $CD4^+$ T cells, which strongly correlated with plasma IL-2.[24] Given STAT5ab/IL-2 signaling is important in T cell differentiation and the development of Tregs, it may be relevant to the maintenance of maternal–fetal tolerance.[24]

In a subsequent study, Aghaeepour et al. investigated whether plasma protein signatures from women having term pregnancies could predict GA and whether functionality of these proteins is

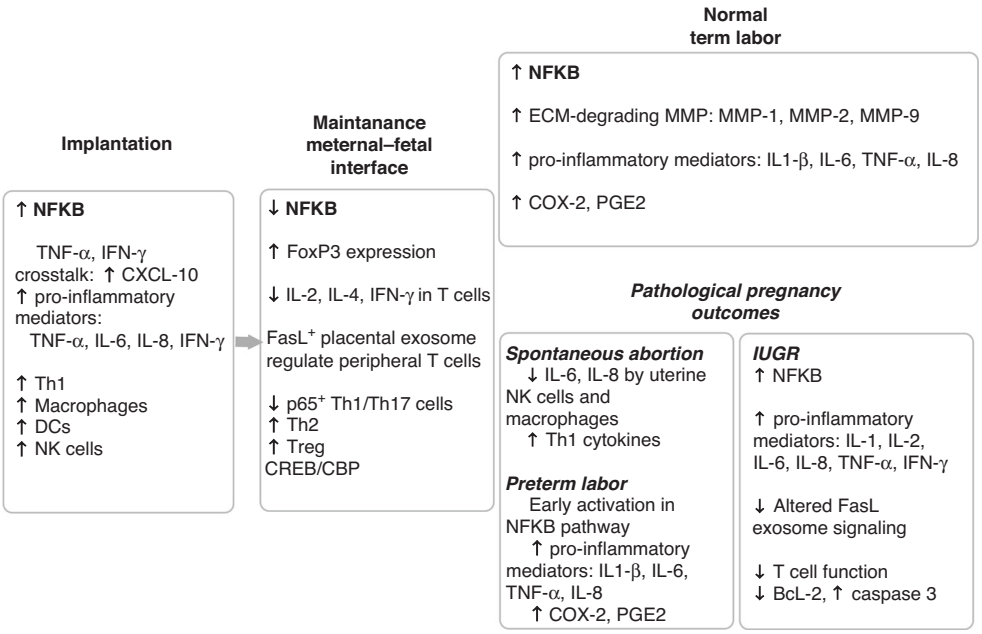

Fig. 2 Inflammatory and immune regulation of healthy and pathological pregnancies. Summary of NF-KB pathway in normal and pathological pregnancies.

associated with pregnancy-related immunologic changes.[25] Three proteins (glypican 3, chorionic somatomammotropin hormone, and granulin) ranked highest out of eight in predicting GA, while chorionic somatomammotropin hormone showed a strong correlation with immunologic changes, specifically in $CD4^+$ T cell STAT5 signaling, suggesting a role in regulating T cell function.[25]

A recent study demonstrated that the onset of spontaneous labor can be predicted by multiomics data integration.[33] The metabolome, proteome, and immunome profiles generated from maternal blood samples longitudinally collected from the last 100 days of pregnancy (i.e., prior to labor onset) were interrogated for prediction of time to spontaneous labor.[33] There was an observed increase in the IL-1 receptor type 4 (IL-1R4) proteomic signature in the last 30 days prior to labor onset along with a decrease in JAK-STAT and MyD88, which suggests the involvement and regulation of late pregnancy inflammatory pathways.[33]

Associated variations in placental methylated DNA (DNAm) and gene expression for several previously established GWAS loci for birth weight were determined using an omics approach.[32] PLEKHA1, FES, PRMT7 and CTDNEP1, were classified as potentially causal to BW.[32] Of these, PLEKHA1, FES and PRMT7 met the cut-off as having a shared causal variant and identified as functional genes for underlying BW, DNAm, and gene expression in the placenta by a multi-trait colocalization test.[32] Importantly, these results were validated in two independent datasets (Table 1).

MAPPING THE HEALTHY DEVELOPMENT OF THE FETAL/NEONATAL IMMUNE SYSTEM WITH OMICS

Development of the human immune system is complex and begins at pre-conception and matures throughout adolescence.[34] Briefly, in humans, the fetal liver harbors lymphocyte progenitors around 7–10 weeks of gestation, followed by progenitor migration to the thymus by week 9, and the initiation of lymphopoiesis in the bone marrow by week 12.[34] During the next 14–26 weeks, an expansion of the T cell pool occurs that coincides with the training of T cells or acquisition of T cell function, and thereby exposing a susceptible window for reprogramming.[34]

Maintenance of a healthy maternal–fetal interface is necessary for the normal development of the fetal immune system (Table 2). Fragiadakis et al. analyzed paired peripheral maternal blood samples and cord blood after cesarean delivery and characterized the maternal–fetal immune cell network and function at term.[27] Using single-cell time-of-flight mass cytometry (CyTOF), an unsupervised clustering algorithm, and scaffold mapping, they found that the neonatal adaptive immune system is enhanced, except for a lower STAT1 response, while the innate immune system is dampened, consistent with earlier reports.[27] More importantly, novel differences were identified between the maternal and fetal immune systems including increased ERK1/2, MAPK-activated protein kinase 2, rpS6, and CREB phosphorylation in fetal $Tbet^+CD4^+$ T cells, $CD8^+$ T cells, B cells, and $CD56^{lo}CD16^+$ NK cells and decreased ERK1/2, MAPK-activated protein kinase 2, and STAT1 phosphorylation in fetal intermediate and nonclassical monocytes.[27]

Peterson et al. collected umbilical cord venous blood samples from neonates born between 25 and 40 weeks of gestation who were not exposed to chorioamnionitis.[35] Innate and adaptive immune cell frequencies and baseline intracellular signaling and responses after stimulation with lipopolysaccharide (LPS), interferon-alpha (INF-α), and a cytokine cocktail, were evaluated using CyTOF to identify specific neonatal immune signatures, and whether GA could be predicted based on these changes alone.[35] Overall, they observed that ligand-specific responses progressively increased in immune cells as GA advanced as opposed to a high basal signaling tone for inflammatory mediators at earlier GAs. Additionally, innate immune cells including neutrophils and classical monocytes increased while Tregs decreased with advancing GA.[35] These findings may constitute a first step to further understand the inflammatory- and infection-related neonatal morbidities seen in preterm neonates across gestation.

INTRA-AMNIOTIC INFECTION (IAI)/HISTOLOGIC CHORIOAMNIONITIS (HCA) AS IMMUNOTOXIC EXPOSURES AND CAUSES OF IMMUNE SYSTEM REPROGRAMMING

An altered intrauterine homeostasis can lead to neuro-immune and peripheral immunologic alterations, and thus can impact long-term health and result in lifelong disabilities.[36–39] Immune system reprogramming in the fetus can occur during critical

Table 1. Determination of a healthy maternal–fetal interface: maternal peripheral blood samples, placentas, and omics data integration.

"Immune clock" of pregnancy	Maternal whole blood:	Aghaeepour et al.
	T cell IL-2-STAT5ab	
Term GA delivery prediction	Maternal plasma proteins:	Aghaeepour et al.
	Glypican 3	
	Chorionic somatomammotropin	
	Granulin	
Onset of spontaneous labor	Maternal blood:	Stelzer et al.
	Decrease in IL-1R4	
	Decrease in JAK-STAT	
	Decrease in MyD88	
Placental multiomics for determining BW	GWAS BW/placental epigenomics and transcriptomics: evidence of mutitrait colocalization for loci with causal sharing between BW, DNAm, and gene expression	Tekola-Ayele et al.
	PLEKHA1 gene expression (GWAS) colocalize with DNAm sites in PLEKHA1 and HTRA1 (Placenta)	
	FES gene expression (GWAS) colocalize with 9 DNAm sites in FES (Placenta)	
	PRMT7 gene expression (GWAS) colocalized with DNAm site in SMPD3 (Placenta)	

IL interleukin, *STAT5ab* signal transducer and activator of transcription 5ab, *JAK* janus kinase, *MyD88* myeloid differentiation primary response 88, *BW* birth weight, *GWAS* genome-wide association study, *PLEKHA1* pleckstrin homology domain containing A1, *DNAm* DNA methylation, *HTRA1* serine peptidase 1, *FES* proto-oncogene tyrosine kinase, *PRMT7* protein arginine methyltransferase 7, *SMPD3* sphingomyelin phosphodiesterase 3.

Table 2. Fetal/neonatal immune system development and reprogramming.

AF, acute HCA	↑ fetal plasma IL-6 independent risk for neonatal morbidity	Gomez et al.
AF, chronic HCA	↑ significantly elevated fetal serum CXCL-10	Kim et al.
AF, IAI	Cell-specific transcriptomic changes strongly correlate with severity of FIRS	Gomez-Lopez et al.
Cord blood at term, **no** HCA	CyTOF/ML ↑ ERK1/2, MAPK-apk2, rpS6, CREB in $Tbet^{+}CD4^{+}$, $CD8^{+}$ T cells, B cells, $CD56^{lo}CD16^{+}$ NK cells ↓ ERK1/2, MAPK-apk2, STAT1 phosphorylation in intermediate and classical monocytes	Fragiadakis et al.
Cord blood 25-40 weeks, **no** HCA	CyTOF/ML↑ basal signaling tone for inflammatory mediators at earlier GA ↑ neutrophil, classical monocytes at later GA ↓ Tregs at later GA	Peterson et al.
Peripheral blood at birth/<24 HOL, HCA-exposed preterm, not infected	Activation of MiR-155-regulated innate and adaptive immune system pathways Differential expression of CCL2/MCP-1, MPO, MMP-9	Weitkamp et al.
Postnatal epigenetic modifications, preterm neonate, no HCA	Monocytes acquire activating histone modification, H3K4me3, near TNF-α, IL1-β, IL-6 gene promoters as PMA advances	Bermick et al.
Postnatal epigenetic modifications, preterm neonate, HCA	Alterations of histone modifications at baseline and after second inflammatory hit	Bermick et al.

AF amniotic fluid, *IL* interleukin, *CXCL* chemokine ligand, *FIRS* fetal inflammatory response syndrome, *ERK1/2* extracellular signal regulated kinase, *MAPK-apk2* mitogen-activated protein kinase, *rpS6* human phosphoribosomal protein S6, *CREB* cAMP response element binding protein, *Tbet* T box expressed in T cells, *CD* cluster of differentiation, *NK* natural killer, *STAT1* signal transducer and activation of transcription 1, *GA* gestational age, *Tregs* regulatory T cells, *MiR-155* microRNA 155, *MCP-1 (a.k.a. CCL2)* monocyte chemoattractant protein-1 (CC motif chemokine ligand 2), *MPO* myeloperoxidase, *MMP-9* matrix metalloproteinase-9, *H3K4me3* tri-methylation at the 4th lysine residue of the histone H3 protein, *TNF-α* tumor necrosis factor alpha, *CCR2* CC motif chemokine receptor 2, *PMA* post-menstrual age, *HOL* hours of life, *ML* machine learning.

immunotoxic prenatal windows during the prenatal period[40] due to exposures to inflammation or infection, and can skew immune responses, thus contributing to disease processes and mortality.[34]

In most HCA cases, clinical illness is not observed in the mother or the fetus.[41–44] HCA becomes more prevalent as the GA at delivery decreases, with 94% of periviable infants shown to have chorioamnionitis.[42] Furthermore, HCA may be present in 36% and 58% in mothers undergoing PTL with intact membranes and in PPROM, respectively.[45] However, major neonatal morbidities, such as neonatal sepsis, respiratory distress, BPD, and white matter injury were more prevalent in infants with fetal inflammatory response syndrome (FIRS).[46–48] Specifically, fetal plasma IL-6 exceeding 11 pg/mL was identified as an independent risk factor for neonatal morbidity.[45] Almost half of the infants with high fetal plasma IL-6 concentrations and adverse neonatal events did not have bacterial invasion of the amniotic fluid or an associated HCA, and thus may only have a sterile inflammation.[45]

In contrast, chronic chorioamnionitis is defined as the infiltration of maternal $CD8^{+}$ T cells into the chorioamniotic membranes

or the chorionic plate.[41,49] The frequency of chronic chorioamnionitis is higher in PPROM, PTL, and preterm deliveries compared with infants born at term.[49] An isolated elevation in amniotic CXCL-10 concentrations has been found to be associated with the subsequent delivery of a placenta with lesions consistent with fetal rejection, but not acute HCA.[50] It is important to note that the degree of elevation of amniotic CXCL-10 concentrations correlated with the severity of chronic chorioamnionitis.[49] Fetal serum CXCL-10 concentration was significantly elevated in cases with chronic placental inflammation and fetal rejection.[51]

All in all, there is still a pressing need to elucidate the mechanism(s) of the reprogramming of the neonatal immune system following immunotoxic exposures where high-dimensional omics approaches can be utilized. Peripheral blood collected at birth from neonates who were exposed to HCA, but not infected, displayed activation of the innate and adaptive immune pathways and with differential expression of certain mediators such as CCL2/MCP-1, MPO, and MMP-9.[37] HCA was found to be associated with miR-155-regulated activation of the innate and adaptive immune pathways in whole blood and CCL2 in plasma samples obtained from moderate to late preterm neonates within 24 h of birth.[37] This was the first study to show gene expression patterns suggestive of immune system priming in preterm infants exposed to HCA.[37] miR-155 is an upstream regulator of these affected immune networks and has been associated with chronic inflammation.[37,52,53] These changes in monocyte transcription and its regulation are hypothesized to contribute to the potential increase in susceptibilities of neonates to postnatal infections and long-term immune system reprogramming and dysfunction in adulthood.[37]

During the maturation of the immune system from neonatal life to adulthood, important epigenetic modifications occur in individual immune cells.[54] Monocytes obtained from preterm neonate blood have less abundant H3K4me3, an activating histone modification, when compared to term neonates and adults. Less abundant H3K4me3 near pro-inflammatory cytokine promoters such as TNF-α, IL1-β, and IL-6 correspond to decreased pro-inflammatory responses in preterm neonates.[54] However, this normal developmental change in histone modification can be altered in the presence of HCA at baseline and after a second inflammatory challenge.[55] In a 2021 study by Gomez-Lopez et al., neutrophils and monocytes/macrophages in the amniotic fluid were isolated by fluorescence-activated cell sorting (FACS) and their origins (maternal or fetal) was determined by DNA fingerprinting.[56] Subsequent cell-type-specific transcriptomic differences in these immune cells from women with IAI showed a strong correlation with the severity of the fetal inflammatory response.[56] Furthermore, the immune transcriptome varied based on the origin (maternal *versus* fetal) of the cell[56] (Table 2). Therefore, early identification of at-risk fetuses and neonates exposed to HCA will be useful in guiding postnatal disease prediction and management.

OMICS APPROACHES TO INTRA-AMNIOTIC INFECTION/HISTOLOGIC CHORIOAMNIONITIS-ASSOCIATED PATHOLOGIC PREGNANCY OUTCOMES

In 2010, Romero et al. published the first metabolomics study of the amniotic fluid to identify patients who presented with PTL but delivered at term, PTL without IAI and delivered preterm, and PTL with IAI and delivered preterm using gas/liquid chromatography and mass spectroscopy (GC-MS).[57] Metabolomic profiling of the amniotic fluid was able to correctly identify patients with 88.5 to 96.3% accuracy, but this technique would require invasive collection, which would limit clinical utility[57] (Table 3). A recent study by Vincente-Munoz et al. focused on the vaginal metabolome to diagnose PTL with intact membranes, since sample collection is minimally invasive.[58] They sought to determine whether the vaginal metabolome could discriminate PTL cases with and without microbial invasion of the amniotic cavity where the current gold standard is amniotic fluid analysis.[58] Using nuclear magnetic resonance (NMR) spectroscopy, they were able to discriminate PTL cases with and without microbial invasion of the amniotic cavity[58] (Table 3).

Fattuoni et al. was able to discern newborns exposed to HCA (mean GA = 30.2 ± 3.8 weeks) from those who were not (mean GA = 30.2 ± 2.9 weeks), based on urine metabolomics signatures in the first 24 h of life by gas chromatography–mass spectroscopy (GC-MS).[59] Among the 29 metabolites that showed a difference, 28 were downregulated, while gluconic acid was upregulated.[59] Furthermore, using a metabolite set enrichment analysis, they showed that energy metabolism-related functional pathways (including glutamate metabolism, mitochondrial transport chain, tricarboxylic acid [TCA] cycle, and galactose, fructose, and mannose metabolism) were significantly affected in newborns whose mothers were diagnosed with HCA when compared with controls.[59] Some limitations of this study were a small sample size and lack of placental and microbial data as microbial flora could have impacted gluconic acid values[59] (Table 3).

It has been recently shown that asymptomatic or mild COVID-19 infections in mothers can result in immune system reprogramming at the maternal–fetal interface in the term placenta[60] (Table 3), but their long-term effects on their infants remains to be seen.[61]

OMICS AND MACHINE-LEARNING APPROACHES TO COMMON SUSTAINED INFLAMMATION-ASSOCIATED NEONATAL MORBIDITIES

Inflammation is associated with many neonatal morbidities,[1] with sustained inflammation specifically associated with BPD, ROP, IVH, and PVL to name a few.[1] Transcriptomic analyses of samples collected from intrauterine inflammation- and postnatal hyperoxia-exposed rat pups have shown that resident immune cells and inflammatory immune pathways in the lung were upregulated at 2 weeks and 2 months postnatally, compared with control rats.[62] In contrast, there was a downregulation of genes in T cell receptor signaling and $CD8^+$ T cell gene expression that persists until adulthood despite recovery to room air.[62] In cord blood of human neonates, exposure to HCA/inflammation not only can alter or activate immune and inflammatory genes, but it also can influence differential gene expression affecting lung development, airway remodeling, neuroimmune pathways, and the development of asthma, allergy, and BPD.[63]

BPD is the most common pulmonary morbidity with life-long sequalae and is prevalent among extremely preterm neonates with a multifactorial pathogenesis.[64] Omics approaches have been applied to study BPD.[65] However, a universally agreed, reliable biomarker for its diagnosis and/or prognostication is not yet available.[66] In a recent review, Piersigili and Bhandari summarized genomics, epigenomics, microbiomics, transcriptomics, proteomics, and metabolomics approaches to BPD in human neonates, including potential BPD biomarkers in tracheal aspirates, urine, or volatile compounds in exhaled breath.[66–71] In a 2011 study by Fabiano et al. tracheal aspirate metabolic profiles analyzed by NMR or GC-MS were different from bronchoalveolar lavage (BAL) fluids collected during mechanical ventilation after administration of surfactant for respiratory distress syndrome (RDS) compared with those collected before surfactant administration.[66,67] Fanos et al. in 2014 showed by using urine samples collected within 24–36 h of life from preterm neonates who were <27 weeks of gestation or <1500 g at birth, it may be possible to identify neonates who will develop BPD by increases in lactate, taurine, trimethylamine-*N*-oxide (TMAO), and myoinositol, or decreases in gluconate.[66,68] Carraro et al. reported observing an altered exhaled breath condensate metabolomic profile by liquid

Table 3. Omics approaches to diagnose inflammation-, MIAC-, IAI-, and HCA-associated pathologic pregnancy outcomes.

PT labor and delivery at term	AF, representative metabolomics: ↑ galactose, hexose cluster 2, 3, 5, 6, mannose, fructose, urea, 3-hydroxybutanoic acid, palmitate, threo-isocitric acid, glycerol, citric acid ↓ alanine, glutamine, pyroglutamic acid, isoleucine, glutamic acid, serine, tyrosine	Romero et al.
PT labor, no IAI with PT delivery	AF, representative metabolomics: ↑ hexose cluster 6, dulcitol ↓ alanine, pyroglutamic acid, proline, glycine, glutamine, galactose, hexose cluster 3, 5, mannose, inositol	Romero et al.
PT labor with IAI	AF, representative metabolomics: ↑ alanine, pyroglutamic acid, glutamine, leucine, proline, isoleucine, valine, glutamic acid, glycine, tyrosine ↓ galactose, hexose cluster 1, 2, 3, 5, 6, mannose, fructose	Romero et al.
PT labor with MIAC, intact membranes	Vaginal, metabolomics: ↑ hypoxanthine, proline, choline, acetyl choline ↓ phenylalanine, glutamine, leucine, isoleucine, glycerophosphocholine	Vivente-Munoz et al.
Distinction of newborn exposed to HCA	Urine, metabolomics: ↑ gluconic acid Alterations in glutamate metabolism, mitochondrial electron transport chain, citric acid cycle, galactose metabolism, fructose and mannose degradation	Fattuoni et al.
Asymptomatic/mild COVID-19	Term decidua: single-cell RNA sequencing Decidual macrophages (HLA-DR^{high}): ↓ frequency, ↑ cytokine signaling, ↑ MHCII Monocyte-derived decidual macrophages (HLADR^{low}): ↓ MHCII, ↓ INF type I signaling, ↑ cytokine signaling Decidual CD4^{+} T cells: ↓ naive subset, ↑ activation, ↓ Treg Decidual CD8^{+} T cells: ↑ terminally differentiated, ↑ exhaustion (PD-1), ↑ INF type I signaling Blood: single cell RNA sequencing ↓ T cell diversity	Sureshchandra et al.

IAI intra-amniotic infection, *MIAC* microbial invasion of amniotic cavity, *HCA* histologic chorioamnionitis, *PT* preterm, *AF* amniotic fluid, *HLA-DR* human leukocyte antigen DR isotype, *MHC* major histocompatibility complex, *INF* interferon, *CD* cluster of differentiation, *Tregs* regulatory T cells, *PD-1* programmed cell death protein 1.

chromatography–mass spectroscopy (LC-MS) in adolescents (mean age of 14.8 years) who were former premature neonates with a mean GA of 28.4 weeks and had BPD when compared with healthy adolescents, suggesting that metabolomics profiles remain altered in later life for infants with BPD[66,70] (Table 4).

In neonates who were born at <30 weeks of gestation, with or without exposure to maternal chorioamnionitis and had RDS, tracheal aspirates collected within the first 24 h of life were studied using LC-MS-based untargeted lipidomics.[72] This study described changes in the lipidomic fingerprints in the fluid of the lung epithelial lining collected from preterm neonates with RDS who had exposures to chorioamnionitis compared with neonates who did not have a clinical presentation of RDS.[72] The authors suggested that the identified tracheal aspirate lipid mediators (Table 4) in neonates with RDS exposed to chorioamnionitis could be associated with later adverse respiratory outcomes. However, RDS at birth does not necessarily correlate with an increased risk of BPD and studies on whether chorioamnionitis contributes to later BPD sequalae have been controversial.[73–77] Whether these omics approaches can shed light on the pathogenesis, prediction, or outcomes of BPD remains to be seen.

Prematurity, chorioamnionitis, antenatal or postnatal infection, and sustained inflammation have been associated with multiple neonatal neurologic morbidities, including IVH, PVL, and cerebral palsy (CP).[78–81] However, it has been challenging to tease out the exact implications of HCA versus clinical chorioamnionitis to infant and/or later school age outcomes.[79–81] Using an LC-MS-based metabolomics approach, Dudzik et al. set out to identify novel pathophysiologic processes for HCA and associated perinatal brain injury in a cohort of pregnant women with PPROM (24 to 32 weeks of gestation) and/or PTL (24–28 weeks).[82] Samples were stratified into neonates with normal neurological findings without any evidence of microbial or HCA exposure (controls), and those with HCA exposure and neurological sequalae defined by presence of PVL or IVH by ultrasound or magnetic resonance imaging (MRI).[82] Sphingolipids, specifically sphingomyelin and lactosylceramides, were significantly altered in the amniotic fluid from infants with chorioamnionitis compared with controls.[82] Notably, lactosylceramides were increased 3000 times.[82] It is important to highlight that sphingomyelin is a sphingolipid present in white matter, while lactosylceramide has proinflammatory and oxidative properties and acts as a second messenger in neuroinflammatory diseases.[82–86] However, in this study, amniotic fluid lactosylceramide levels were not predictive of perinatal neurological sequalae for neonates of women with chorioamnionitis.[82] Therefore, the authors concluded that amniotic fluid lactosylceramides could be used as a biomarker for chorioamnionitis, but not predictive of later neurological sequalae, specifically IVH[82] (Table 4).

A genome-wide association study (GWAS) of neonates who were born $25^{0/7}$ to $29^{6/7}$ weeks of gestation, <1500 g, and who had a history of minimum 3 days of intermittent positive pressure ventilation, did not identify any clinical chorioamnionitis-associated single nucleotide polymorphisms (SNPs), but highlighted an association between clinical chorioamnionitis, high-grade IVH, PVL, and high-grade ROP[87] (Table 4).

In a recent study, Hamilton et al. demonstrated that using a supervised machine-learning approach can outperform traditional statistical methods in identifying discriminating factors for a known outcome.[88] In neonates born at $23^{0/7}$–$31^{6/7}$ weeks of gestation, a composite outcome including severe IVH (grade 3 or 4), ventilator dependence ≥28 days, PVL, surgical necrotizing enterocolitis (NEC), death and clusters with known antenatal risk factors were identified.[88] Utilizing logistic regression, machine-learning algorithms or a hybrid model that utilizes both methods, they predicted severe morbidity. Babies who had abnormal fetal

Table 4. Omics and machine-learning approaches to common sustained inflammation associated neonatal morbidities.

BPD, biomarker	Tracheal aspirate: ↑ undecane, decanoic acid, dodecanoic acid, hexadecenoic acid, octadecanoic acid, hexadecenoic acid methyl ester, 9-octadecanoic acid, tetracosanoic acid, myristic acid, phosphate	Fabiano et al.
BPD, biomarker	Urine: ↑ lactate, taurine, trimethylamine-*N*-oxide (TMAO), and myoinositol ↓ gluconate	Fanos et al.
BPD, biomarker	Volatile compounds: lyso-phosphatidylcholine, platelet activating factor (PAF), unsaturated phosphatidyl choline, plasmenyl-phosphatidylserine	Carraro et al.
RDS, lipidomics, PT with/without exposure to chorioamnionitis	Tracheal aspirate: ↑ glycerophospholipids, sphingolipids ↓ sphingomyelins	Giambelluca et al.
HCA, biomarker, not predictive of IVH	AF: ↑ sphingomyelin, lactosylceramide	Dudzik et al.
Clinical chorioamnionitis associated SNPs or outcomes	GWAS bloodspots: No clinical chorioamnionitis associated SNPs identified in preterm Association with high-grade IVH, PVL, high-grade ROP sustained	Spiegel et al.
ROP, biomarker	Cord plasma: Severe ROP/laser treatment: ↑ IL-6 ↑ C5a	Park et al.
ROP, biomarker	PT serum: Severe ROP: PILRB Negative correlation with ROP: HBEGF, CD84, AGER, SERPINE1, ANGPT1, APP, MMP-12, PPIB, GDF2, THBD, CD40LG	Danielsson et al.

BPD bronchopulmonary dysplasia, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *ROP* retinopathy of prematurity, *PT* preterm, *HCA* histologic chorioamnionitis, *AF* amniotic fluid, *PILRB* paired immunoglobin-like type 2 receptor beta, *RDS* respiratory distress syndrome, *GWAS* genome-wide association study, *SNP* single-nucleotide polymorphism, *HBEGF* heparin binding EGF-like growth factor, *CD* cluster of differentiation, *AGER* advanced glycosylation end product-specific receptor, *SERPINE1* plasminogen activator inhibitor-1, *ANGPT1* angiopoietin-1, *APP* amyloid beta precursor protein, *MMP* matrix metalloproteinase, *PPIB* peptidylprolyl isomerase B, *GDF2* growth differentiation factor 2, *THBD* thrombomodulin.

testing, IUGR, who were born before 28 weeks and had incomplete antenatal steroid course were at highest risk.[88] The hybrid approach yielded an area under the curve (AUC) of 0.85[88] demonstrating that a hybrid model can potentially identify factors that are not linear or independent, but are composed of a collection of etiologies.[88] However, this study did not identify any novel risk factors.

ROP is a preterm birth-related cause of blindness. The pathophysiology of ROP is related to abnormal vascular development at the boundary of a vascularized and an avascular peripheral retina. Early GA at delivery, low BW, and higher or variable levels of oxygen supplementation are major risk factors for the development of ROP. In a retrospective cohort study of 110 premature singleton infants who were born at ≤32.0 weeks of gestation, cord plasma at birth was assayed for various biomarkers.[89] The primary outcome measures were the occurrence of any stage ROP, severe ROP (>stage 3), and vision-threatening type 1 ROP requiring laser treatment. ROP was diagnosed in approximately 27%, of which 12% was with severe ROP.[89] Laser treatment was performed on 6.4%.[89] A prediction model was developed, which included high cord plasma IL-6 levels and low BW for severe ROP (AUC of 0.84), and high cord plasma C5a levels and low BW for laser treatment (AUC of 0.884). The authors concluded that elevated levels of cord plasma IL-6 and C5a could be used as independent biomarkers to predict severe ROP and laser treatment, respectively[89] (Table 4).

Danielsson et al. identified serum proteins that correlated with later ROP from extremely preterm neonates using a novel multiplex extension proximity assay platform.[90] Using hierarchical clustering and principal component analysis (PCA), they computed pairwise Spearman correlations on blood samples that were longitudinally collected from 14 extremely preterm neonates at several timepoints including at birth, postnatal weeks 1, 2, 4, and post-menstrual age (PMA) 32, 36 and 40 weeks.[90] Among 448 unique target proteins that were analyzed from 88 patient blood samples, 20 most significant proteins were identified that correlated with GA and/or ROP.[90] The levels of 11 out of these 20 proteins showed a direct correlation to ROP, but not to GA.[90] Furthermore, they correlated the function of ROP-associated proteins to angiogenesis, neurogenesis, osteogenesis, immune function, and lipid metabolism.[90] Although these findings raise hope for identifying disease-specific biomarker to predict ROP severity, they need validation in larger cohorts[90] (Table 4).

OMICS AND MACHINE-LEARNING APPROACHES IN IMMUNOPERINATOLOGY AND NEONATOLOGY

Current state

Methodological advances have enabled an exponential increase in omics data that interrogates pregnancy and maternal-placental-fetal interactions. High-dimensional functional immune profiling with novel analytic algorithms unraveled the exact immune changes that occur during the time course of normal term pregnancy as well as dyads of mothers and their respective newborns at term.[24,27] Furthermore, combining state-of-the-art multiomics datasets (such as maternal metabolomics, proteomics, and immunomics) have revealed that these systems are interconnected in determining onset of labor in term and preterm pregnancies.[25,33] In a recent study, more than 500 members of computational biology community were assembled and challenged to predict GA and spontaneous preterm birth using whole blood transcriptomic and/or plasma proteomic profiles using data

obtained <37 weeks of gestation and samples collected from asymptomatic pregnant women <33 weeks.[29] This approach accurately predicted delivery dates in spontaneous preterm and term births, identified a leukocyte-mediated immunity gene expression signature for PPROM and correctly estimated ultrasound-based GAs.[29] Prediction of preterm birth by transcriptomics/plasma proteomic profiles could be beneficial for identifying at-risk pregnancies for targeted therapies.

It has been difficult to differentiate associations from causality for most neonatal morbidities. Approaches integrating omics datasets into machine-learning algorithms may prove beneficial for unbiased prediction tools for common neonatal morbidities to enable timely interventional strategies and alleviate adverse outcomes.[91,92]

Limitations

It is important to acknowledge some of the limitations of omics approaches. While omics technologies provide sophisticated datasets, understanding the underlying pathophysiology of a disease may be challenging. Inflammatory, immune biomarkers in peripheral blood may not be directly causal in the pathophysiology of inflammatory-immune-organ injury. Furthermore, while the machine-learning methods discussed in this manuscript can identify important associations, they cannot, in general, make inference about causal effects. Despite the advantage that omics technologies can quantify a vast amount of markers, sample sizes in individual studies are still small which necessitate further studies to validate and evaluate the rigor and reproducibility of existing neonatal omics studies. Analysis of such data with high number of features and small sample sizes requires specific machine-learning methods that can effectively identify the most important biomarkers and results in fairly simple models.[93] Over-complicated models can lead to overfitting the data and poor generalization.[93] Furthermore, any novel pathways identified as potentially causative for pregnancy-related pathologies or neonatal morbidities should be further studied and confirmed in relevant animal models and then used to guide potential therapeutic strategies.

Advancing the field

An in-depth understanding of the normal dynamic changes in pregnancy, integration of all available clinical, multiomics datasets with machine learning can pave the way for future research on the causes of preterm birth including infection/inflammation-related immunologic alterations to pregnancy complications, and immediate neonatal and long-term adverse outcomes.[2,26,91] Statistical learning methods can be applied to predict neonatal outcomes from prenatal maternal data and additional neonatal information that becomes available during NICU course.[28] Collective knowledge gained by interrogating the maternal and neonatal immunome along with other omics data can delineate inherent susceptibilities of each maternal/neonatal dyad and guide individualized treatment approaches for inflammatory/infectious morbidities in premature neonates.[35] Validation studies with larger sample sizes can evaluate the rigor and reproducibility of current data and advance the field. Additionally, by expanding the sample sizes, generating centralized databanks and better integration of machine-learning approaches, causal pathways in neonatal diseases might be unraveled. In the future, merging antenatal maternal and postnatal neonatal omics data, real-time clinical data and application of machine-learning algorithms to identify most at risk neonates for precision care will help with timely interventions and treatment.[94–97]

DATA AVAILABILITY

Data sharing not applicable to this article as no datasets were generated or analyzed for this review.

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AUTHOR CONTRIBUTIONS

M.O., N.A., I.M., R.J.W., D.K.S., and L.L.J. contributed to the writing and approval of the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No patient consent was required for this review.

ADDITIONAL INFORMATION

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