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Review

Heart care before birth: A psychobiological perspective on fetal cardiac diagnosis

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ABSTRACT

Fetal diagnosis of congenital heart disease (CHD) is often associated with profound psychological stress for expectant mothers and fathers. Decades of research shows high levels of maternal prenatal stress may affect fetal brain-behavior development and influence children's neurobehavioral trajectory, potentially increasing their risk of adverse physical and mental health outcomes later in life. While a range of factors may contribute to neurobehavioral vulnerability in children with CHD, a developmental psychobiological perspective offers a compelling avenue for investigation and intervention. Underlying pathways by which maternal prenatal stress may influence fetal and child neurobehavioral development include, but are not limited to, altered hypothalamic-pituitary-adrenal (HPA) axis functioning, inflammation, placental epigenetic effects, altered microbiome or telomere biology, and maternal health behaviors. Optimal heart care before birth requires equal emphasis on the physical and the psychological, and includes targeted, evidence-based strategies to support parent, child and family wellbeing across a lifetime. Health policies prioritizing mental health care in fetal and pediatric cardiology, and robust trials testing the efficacy of interventions to buffer the effects of early medical adversity, are important next steps.

In the United States and around the world, the landscape of congenital heart disease (CHD) care is rapidly evolving. With advances in medicine, survival has markedly improved over the past two decades [1] and best estimates suggest the total population, from newborns through to adults living with CHD, now represents over 2.4 million Americans [2]. These gains in survival are a triumph, but they bring new challenges. Earlier diagnosis, a growing understanding of the genomic contributions to CHD, more complex treatment choices, and the late effects associated with longer survivorship all lead us into new territory. Focusing on *heart care before birth*, this paper presents a psychobiological perspective on fetal cardiac diagnosis, highlighting current knowledge as well as areas where evidence is lacking, and calling for greater investment in research to uncover the mechanisms that contribute to neurobiological risk and resilience in children and adults with CHD.

1. Heart care begins before birth: the mental health of expectant parents

Increasing numbers of babies who need heart surgery in their first year of life are now diagnosed in utero, most before 24 weeks gestation [3,4]. Fetal diagnosis of CHD allows potentially unstable newborns to be delivered close to specialized pediatric cardiac services, reducing morbidity and, for some anomalies, improving the chances of survival [5,6]. Fetal diagnosis also facilitates proactive family counseling regarding the nature of the baby's heart condition and prognosis [7]; yet for expectant parents, this is often a time of intense sadness, fear, anger and grief - emotions which tend to endure throughout the remainder of the pregnancy and well beyond infant hospital discharge [8–13].

Threats to the health of the fetus have long been recognized as an important risk factor for psychiatric disturbance in the perinatal period. Extensive research documents the high levels of stress and distress mothers and fathers experience as a result of their baby's cardiac diagnosis and hospitalization, particularly in the perioperative phase [14–16]. In a recent review of mental health outcomes across various

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time-points after CHD diagnosis ($N = 30$ studies) [14], 25–50% of parents of children with complex CHD reported clinically-elevated symptoms of anxiety or depression, and 30–80% reported severe psychological distress [10]. These rates far exceed national norms [17,18]; yet, the severity and consequences of these symptoms are often substantially underestimated by healthcare providers [19]. Parents with higher distress report poorer physical health [11], greater parenting burden [20], higher health service use [21], more suicidal ideation [18], and poorer quality of life (for both themselves and their child) [22,23] compared to parents of sick children with lower distress. Experiencing anxiety or depression can also interrupt the developing bond between parent and baby, with potential implications for later child attachment, and emotional and neurobehavioral development [24–28].

2. Neurobehavioral and emotional outcomes in children with CHD

In infants with complex CHD, neurodevelopmental delays are common [29–34]. Fine and gross motor skills and early regulatory behaviors may be most affected in infancy, whereas other difficulties – particularly in adaptive, social, emotional, cognitive and executive functioning – may not become apparent until later in childhood [30,31,35–39]. A substantial proportion of parents also report significant 'internalizing' (e.g. anxiety, depression, somatisation) or 'externalizing' (e.g. aggression) difficulties in their child [32]. Adolescents with single ventricle CHD, for example, have a 5-fold increase in the rate of lifetime anxiety diagnoses (35% in SVCHD, 7% in referent group), and an almost 6-fold increase in the rate of lifetime attention deficit hyperactivity disorder (ADHD) diagnosis (34% in SVCHD, 6% in referent group) [40]. Studies in other CHD groups also report a higher prevalence of psychiatric diagnosis compared to normative data [41–43], and only a small proportion of these children and young people receive psychotherapy [41] or neurodevelopmental evaluation [44]. While the precise mechanisms underlying heightened vulnerability to adverse mental health outcomes in children with CHD are yet to determined, a range of factors may contribute, including genetics, disease complexity and comorbidity, prematurity, use of mechanical support, cardiopulmonary resuscitation or peri-operative seizures, stroke, and greater length of hospital stay [30,31,45–49]. The fetal programming model also offers a compelling avenue for investigation and intervention.

3. A psychobiological model of risk and resilience

Since the seminal work of British epidemiologist, David J. Barker [50–56], much has been done to elucidate the *fetal* [57] or *developmental* [58] *origins of health and disease*. Central to Barker's theory is the notion that environmental factors (such as maternal malnutrition) can, during critical or sensitive periods in fetal development, influence the developing structure and function of offspring biological systems, with potentially enduring effects for health or disease across the lifespan [54,59,60]. These systems include the central (CNS) and autonomic nervous systems (ANS), as well as the neuroendocrine (hypothalamic-pituitary-adrenal or HPA axis), cardiovascular, and immune systems [57,61–69]. Developmental or adaptive 'programming' has emerged as a major model for understanding the early origins of health outcomes [70]. The model proposes that in utero exposures instigate an adaptive response in the fetus that carries forward in development with persisting effects on biology and behavior. Responses (such as alterations in HPA-axis functioning, immune activation, placental epigenetics, neural connectivity, and the microbiome) [71–74], in interaction with genetics and postnatal environmental factors, may influence vulnerability to disease. Evidence for the model as applied to cardiovascular outcomes in adulthood is substantial, derived from numerous large-scale studies in diverse settings, and generating a robust line of research because of its potential to influence the health of populations in developed and developing countries [75].

3.1. Fetal origins of mental health

Building on the fetal programming model for physical health, is a burgeoning line of inquiry into how this model may be applied to mental health. These studies focus predominantly on maternal prenatal psychological stress (including perceived stress, stressful life events, depression and anxiety) as a putative causal agent initiating a developmental programming response [69], and follow decades of experimental animal studies linking maternal prenatal stress to sizable and lasting effects on offspring fear, neurogenesis, immunity and stress physiology, among other outcomes [76,77]. In an extensive systematic review of human studies carried out between 2010 and 2017, van den Bergh et al. [69] found that maternal distress across various gestational time-points was associated with offspring neurobehavioral and emotional outcomes, including anxiety and depression, from birth through to adulthood. A powerful example is the Avon Longitudinal Study of Parents and Children (ALSPAC); a 14-year prospective study undertaken in West England, reporting on the developmental outcomes of 7944 children on five occasions from age four to 13 years [70]. Findings from this large community cohort showed that high levels of maternal anxiety and depression during pregnancy were associated with lasting, clinically and statistically significant adverse effects on child behavioral and emotional outcomes, including a two-fold increase in risk of probable mental disorder in boys and girls at ages 4, 7, 9, 11 and 13 years – even after adjusting for multiple confounders, such as infant birth weight, gestational age, maternal age, education, socioeconomic status, substance use in pregnancy, parenting style, paternal prenatal anxiety, and maternal and paternal postnatal anxiety and depression [70]. Results of the ALSPAC study are compelling; the impact of maternal prenatal anxiety and depression on child behavioral problems did not weaken over time, despite the pronounced psychological and biological changes that occur during this decade of life.

There is also converging evidence from both neurocognitive assessments and measures of neural activity, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), demonstrating that prenatal maternal anxiety or depression is associated with altered brain-behavioral development in offspring, including atypical attention [78–80], impulsivity [81] and endogenous cognitive control [82,83], as well as alterations in the developing connectome [84], or structural and functional networks in the brain [85–87]. There is, however, a lack of specificity with respect to the effects of gestational timing of prenatal maternal distress and differentiated child outcomes [69]. Some research suggests the first trimester [79] or first half of pregnancy [79,80,82,87] may be the most vulnerable period in terms of fetal and infant neurobiological outcomes, but few studies have systematically assessed maternal psychological responses across pregnancy to identify one period as influential [88]. Research into potential sex differences has also yielded inconclusive results. Some studies, for example, have found boys' cognitive functioning is more affected by prenatal exposure to maternal stress than girls' [78,89], while others have identified more compromised mental health outcomes in girls [86,90], or comparable magnitudes of sex effects with differentiated outcomes (e.g., greater risk of ADHD in young boys and emotional dysregulation in young girls) [70]. Understanding the influence of factors such as sex and gestational timing of exposure is critical to characterizing prenatal programming processes and neurobehavioral trajectories, and while much remains to be discovered, prospective cohort studies investigating these associations in CHD are underway [10].

If the high levels of parental prenatal stress elicited by fetal cardiac diagnosis do have unintended consequences for fetal and child brain-behavior development, we have an obligation to understand these 'off-target' effects of our well-intended and effective early interventions to improve CHD outcomes. Whether maternal prenatal distress exerts 'programming' effects on the developing fetus through increased exposure to glucocorticoids (via altered HPA axis functioning) [91,92],

inflammation [93], alterations to the placenta [94,95], microbiome [96] or telomere biology [97], maternal health behaviors (e.g., poor nutritional intake or nicotine, drug or alcohol use) [98], sensory experiences [99–101], a combination of these exposures [88], or factors yet to be identified, is an area of active investigation, with a keen focus on determining causal pathways and potential interventions. Research focused on the role of the placenta as a biological mediator [102] between fetal exposures and postnatal outcomes in CHD [103] as well as in mental health is rapidly accumulating, particularly the role of placental epigenetic effects on neurodevelopmental programming [104].

3.2. Opportunities for intervention: Can we 'buffer' the fetus from the effects of prenatal stress?

A key question is whether the fetal programming model may facilitate opportunities to prevent or 'buffer' the developing fetus from the potential effects of prenatal stress and if so, how? The hypothesis that there are fetal programming effects for mental health outcomes in CHD, including neurodevelopmental sequelae, has implications for both the type and timing of interventions. Interventions beginning in the early postpartum period to promote parental mental health, attuned parenting and infant–parent attachment security, are grounded in research linking the quality of the early postnatal rearing environment and child behavioral, emotional, and cognitive development [105–107]. If parent mental health in the prenatal period is also shown to have a causal role, then psychological interventions offered during pregnancy, a currently uncommon practice, may be transformative. The policy implication is that early interventions to prevent child emotional and neurobehavioral disorders - major morbidities in CHD that have a substantial public health cost [108] - could begin in pregnancy by targeting maternal and paternal psychological wellbeing.

In a recent systematic review [109] examining the efficacy of mental health interventions for parents of infants with CHD requiring intensive care unit admission, only four interventions tested in a controlled trial (1 randomized [110], 3 non-randomized [111–113]) were identified. While each intervention had a distinct therapeutic approach (parent-infant interaction [111], psycho-education and parenting skills training [112], early pediatric palliative care [110], family-centered nursing [113]), all demonstrated efficacy in reducing maternal anxiety, although the quality of evidence derived from these trials was low and none of the interventions were initiated during pregnancy [109]. Notably, one trial of a parent-infant interaction intervention demonstrated benefits for infant mental (but not psychomotor) development at 6 months [111]. This finding is important given the high risk of neurodevelopmental deficits in children with complex CHD [31,49], and provides a platform for future research investigating the potential mechanisms of, and potent vehicles for, sustained effect.

While there are data demonstrating the efficacy of psychological interventions delivered during pregnancy in reducing maternal anxiety, depression or stress, very few trials have included pregnant women who receive a fetal cardiac diagnosis [114]. One small study, carried out in Brazil, included a sample with mixed fetal diagnoses (only nine pregnant women with a fetal cardiac diagnosis), and showed improvements in maternal anxiety and depression, but did not examine any fetal or infant outcomes. Outside of CHD, very few studies have examined the potential for prenatally-delivered psychological interventions to generate change in fetal epigenetic profile, or later child physical or mental health outcomes [114]. Rigorous controlled trials of early interventions designed to reduce maternal anxiety and depression during pregnancy, while also examining potential effects for fetal and child neurobehavioral and emotional development, are much needed to inform clinical practice in our field.

4. New frontiers in the field

There is widespread agreement that data on the association between parental prenatal stress after fetal cardiac diagnosis and child neurodevelopmental and mental health outcomes are urgently needed [7,10,115]. Longitudinal studies testing the ways in which genetic, epigenetic and other potential factors may mediate or moderate associations between maternal stress in pregnancy, fetal structural and functional brain connectivity [87,116], and child neurobehavioral outcomes are lacking in CHD [84,117,118]. While it may be difficult to disentangle the effects of prenatal stress exposure from shared genetic risk, recent studies in the broader literature have assessed the effects of maternal prenatal distress while controlling for maternal psychiatric history (as a proxy for genetic vulnerability) and demonstrated an independent effect of prenatal stress on children's risk for psychopathology [119]. Carefully-designed longitudinal studies assessing parental mental health alongside the health outcomes of their children with CHD (or other critical or chronic illnesses), using validated psychobiological measures [120], are thus a high priority.

Anxiety and depression often co-occur and research is also needed to disentangle whether the biological changes associated with maternal anxiety are distinct from maternal depression, and whether these different symptom clusters do or do not share overlapping mechanisms of impact for fetal development and child outcomes. Future studies also need to consider the potential impact of gestational timing of any intervention (which would be limited by the timing of fetal cardiac diagnosis), as well as the dose-response relationship. In terms of gestational timing, potential psychobiological effects are likely to differ for various outcomes according to when specific regions of the brain associated with emotion regulation or memory (e.g., the amygdala and hippocampus) may be at their most vulnerable. There is also evidence that some infant outcomes linked with maternal prenatal stress, such as morphological changes (e.g., cleft lip and palate), seem more sensitive to earlier stress exposure [121]. In terms of the dose-response relationship, there are a small number of studies (outside of CHD) that suggest a moderate degree of maternal prenatal stress may infer slight adaptive 'advantages' for child outcomes - whether that stress is psychological [122–125] or the result of maternal exposure to adversity [126,127]. Additionally, assessing and controlling for the extent to which postnatal influences on children's development may be associated with maternal prenatal stress is enormously challenging. Studies incorporating biobehavioral techniques, such as ecological momentary assessment via electronic monitoring [128,129], may provide one avenue for overcoming this challenge, though feasibility and acceptability among pregnant women and their families must be tested.

4.1. Robust, high-quality integration of mental health services in fetal cardiology

Health policies prioritizing mental health care in fetal and pediatric cardiology, and research investigating the pathways via which parental prenatal stress influences child outcomes, are important next steps. Robust trials testing the efficacy of interventions to buffer the effects of early medical adversity are also much needed. Many countries have shown leadership in this area, with numerous initiatives demonstrating strong community and government engagement to bolster mental health services for children and families affected by CHD. Examples include Australia's National Strategic Action Plan for Childhood Heart Disease [115], the Congenital Heart Public Health Consortium workgroup on Neurodevelopment, Cognitive and Psychosocial Quality of Life (CHPHC CNP-Q) supported by the American Academy of Pediatrics (AAP) and the Centers for Disease Control and Prevention (CDC) [130], and care consensus recommendations from the Association for European Paediatric and Congenital Cardiology (AEPC) Psychosocial Working Group [131]. All such initiatives have a unified focus on addressing knowledge, practice and policy gaps, and utilize public health principles to affect change in the mental health outcomes of children with CHD and their families.

Culturally- and developmentally-sensitive mental health screening

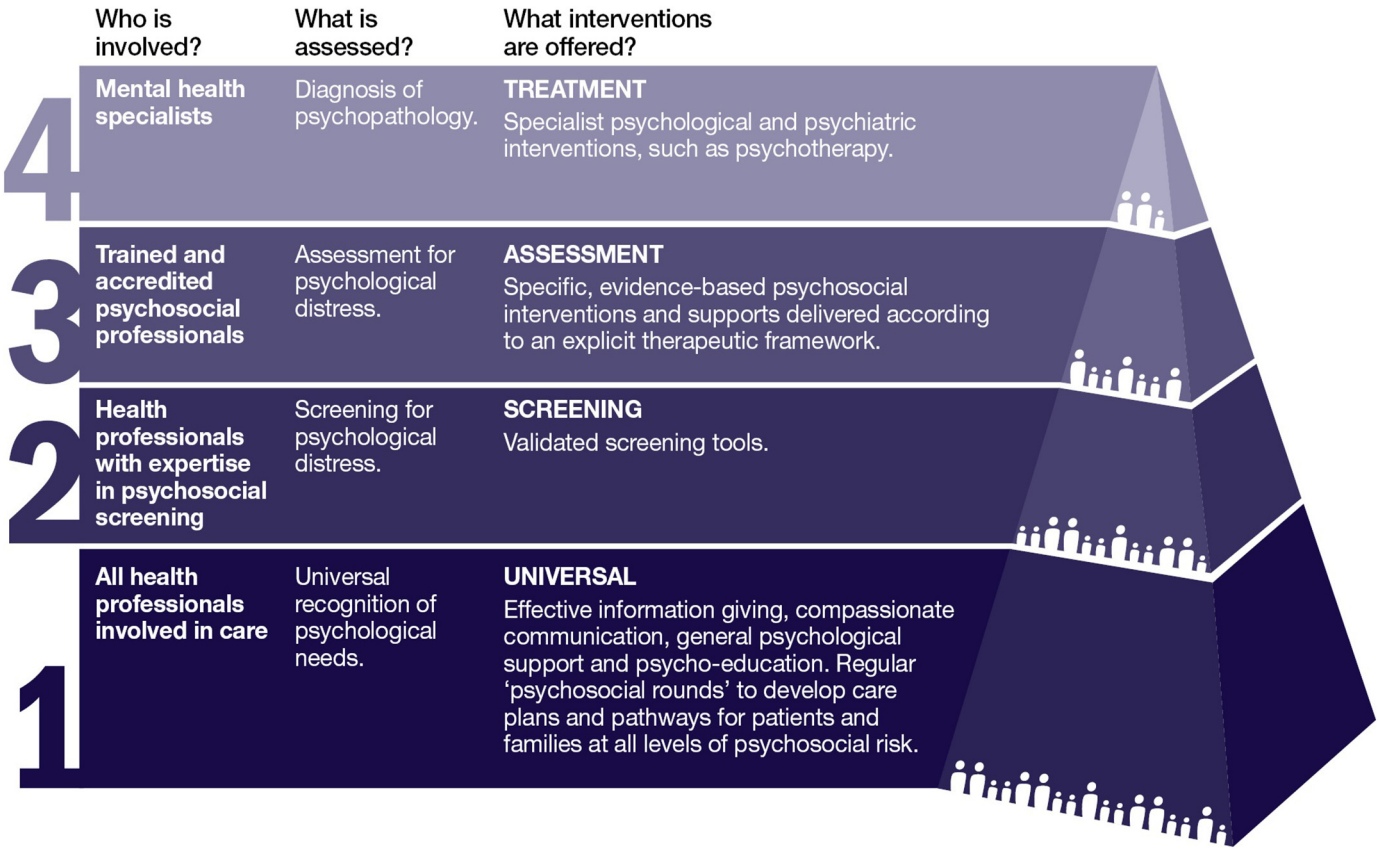

Fig. 1. Four-tier model of integrated mental health screening, assessment and care for all families of patients (from fetus to adult) with congenital heart disease, implemented at the Heart Centre for Children, The Sydney Children's Hospitals Network, Sydney, Australia and originally published in *The Medical Journal of Australia* [10].

and assessment, including neurocognitive assessment across the life course using validated tools, is recommended to facilitate early detection of risk and resilience factors, and to maximize opportunities for responsive, individualized care (Fig. 1) [10,22,132]. Integrated interventions that view early medical adversity through a psychobiological lens, and that are considered part of 'standard' or routine care, are likely to have the broadest impact [10,132–134]. While there may be important patient (e.g. stigma, cost), clinician (e.g. limited awareness, low confidence), and health system (e.g. cost, under-prioritization) factors that serve as barriers to the implementation of such initiatives, these are not insurmountable and the benefits of intervention are very likely to strongly outweigh the obstacles. Diversity and representation in clinical research samples is another ethical and scientific imperative, particularly given the well-documented effects of race and ethnicity on disease risk and treatment response.

5. Conclusion

There is widespread awareness of the mental health needs of children with CHD and their families, and an emerging understanding of the ways in which psychobiological factors can influence health outcomes throughout life. Decades of research shows maternal prenatal stress can affect fetal brain-behavior development and influence children's neurobehavioral trajectory, potentially increasing their risk of adverse physical and mental health outcomes. While a range of factors may contribute to emotional and neurobehavioral vulnerability in children and adults with CHD, a psychobiological perspective offers a compelling avenue for investigation and intervention. Longitudinal studies led by interdisciplinary teams are now needed to deepen our knowledge of the underlying pathways to neurobehavioral risk and resilience for people with CHD. Potential avenues for further investigation include, but are not limited to, HPA axis dysregulation, variation in fetal structural and functional brain connectivity, and alternations in placental gene methylation and the microbiome. Optimal heart care before birth requires equal emphasis on the physical and the psychological, and includes targeted, evidence-based interventions to support parent, child and family wellbeing across a lifetime.

Declaration of Competing Interest

No relevant disclosures.

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