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Preterm birth: High Vulnerability and no Resiliency?

Dieter Wolke

University of Warwick, Department of Psychology and Warwick Medical School, Coventry,

UK

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Correspondence: Professor Dieter Wolke
Department of Psychology
University of Warwick
Coventry
CV4 7AL
United Kingdom

Telephone: +44 24 7657 3217,
Email: D.Wolke@warwick.ac.uk

Globally, 15 million babies are born preterm (< 37 weeks gestation) each year, representing 11% of all live births. In the UK, around 7% of children are born preterm each year and around 15% of all preterm born are born more than 8 weeks early (VPT; very preterm) or below 1500g birth weight (VLBW). Prematurity is the major cause of infant mortality despite largely increased survival in recent decades attributable to advances in antenatal and neonatal care. Very and extremely preterm born infants (EPT; <28 weeks gestation) often spend many weeks and months in neonatal care before discharge. The costs for initial neonatal care of the smallest of infants are in the hundreds of thousands of dollars or UK Pound Sterling and they are much more likely to be readmitted to hospital and require higher health care support in childhood. Although preterm or low birthweight infants account for 7% of births, they account for 37% of the total health service costs for infants in the first year of life (Thanh, Toye, Savu, Kumar, & Kaul, 2015) .

There is now convincing evidence that preterm birth is associated with increased risk for adverse cognitive development, mental health, academic achievement, social relationship problems and poorer quality of life during childhood and adolescence (Johnson & Wolke, 2017). Many of these functional deficits continue into adulthood and adversely affect preterm born individuals' life chances and socio-economic situation (Bilgin, Mendonca, & Wolke, 2018). Prematurity is a growing public health concern as more very preterm babies will enter society each year as birth rates and survival rates continue to increase, while no comparable improvements in functional outcome have been documented (Cheong et al., 2017).

The major focus of previous research has been on risk factors, i.e. the investigation of gestation, birth weight and associated neonatal complications and neonatal treatment

advances on health and developmental outcomes. The intervening time between risk factor exposure and later outcome has often been treated like a “black box”. Assessing what was coined four decades ago as the “continuum of caretaking casualty”, i.e. the influences of caretaking and social factors along development, has often been neglected in medical follow-up studies of VPT/VLBW children. However, the effects of childhood social influences are massive. For example, being born into a high socio-economic status (SES) family compared to one of low SES creates a similar difference in IQ in adulthood as being full term compared to being born VPT (Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015). High SES has been found to be a general promotive factor with similar positive effects on IQ in both VPT/VLBW and term born children.

Resilience, in contrast, refers to beating the odds under conditions of high risk for adverse developmental outcome (Luthar, Cicchetti, & Becker, 2000). These individuals with or exposed to protective factors have better outcomes than others who have experienced a comparable level of adversity but lacking “resiliency”. Resilience may thus indicate a reduced vulnerability to environmental risk experiences or a relatively good outcome despite risk experiences. Resilience may refer to a moderation effect, with those born at risk disproportionately benefitting from a protective factor, such as positive parenting. With a few exceptions (Wolke, Jaekel, Hall, & Baumann, 2013) (Poehlmann-Tynan et al., 2015), there has been a complete absence of identifying factors that may explain why some VPT/VLBW born at similar neonatal risk develop adaptively while others don’t.

The study by van Lieshout (2018) investigates how additional risk factors during childhood and adolescence (e.g. overprotective parenting, physical sexual abuse, peer victimization) as well as protective factors or “resiliency factors” (e.g. number of close friends, academic

achievement in mathematics, caring parenting) may modify the relationship between extreme low-birth-weight (ELBW<1000g) and depression in adulthood compared to a normative birth weight control group (NBW). Their findings provide no evidence that ELBW benefited from any protective factor in reducing the risk of developing depressive symptoms. Thus according to the definition of resilience (Luthar et al., 2000), there was no evidence for protective factors that buffered the risk of ELBW on outcomes, or promotive factors that increased positive outcomes regardless of risk status. Rather, only in the low risk NBW group did “resiliency” factors have an effect on reducing depression symptoms in adulthood. On the other hand, they found that each additional childhood risk factor increased the risk of adverse outcome more in the ELBW than in the NBW group. Van Lieshout et al. (2018) interpret this finding as ELBW exhibiting increased sensitivity to the deleterious effect of childhood risk factors but are less sensitive and thus not protected by resiliency factors. They consider this as support for the developmental origins of health and disease (DOHaD) theory that “exposure of traditional prenatal adversity amplifies the impact of traditional risk factors for depression and anxiety in adulthood” (p. 599).

This finding is intriguing as it indicates a higher vulnerability to additional childhood risk but a muted response to protective or promotive factors throughout childhood. This provides a disheartening message. Are ELBW on an inevitable trajectory for depression symptoms and not able to bounce back? How does this finding sit within the context of other research?

These findings are consistent with others in the literature that looked at other outcomes in childhood or adolescence, namely, academic achievement (Wolke et al., 2013) (Jaekel, Pluess, Belsky, & Wolke, 2015) or functioning within the normal range in a variety of behavioural and emotional outcomes, i.e. following a resilient trajectory (Poehlmann-Tynan

et al., 2015). These three studies all reported on directly observed parenting. Wolke et al. (2013) studied the effect of directly observed maternal sensitivity at 6 years during a standard mother-child interaction task on academic achievement at 13 years of age in VP/VLBW compared to NBW. This study found that when maternal sensitivity was low VP/VLBW did very poorly in academic achievement compared to NBW who were much less vulnerable to poor parenting. A similar finding was found for reading, math, and writing and spelling abilities for both VLBW and LBW compared to NBW by Jaekel et al (2015). Parents of LBW/VLBW are not less sensitive in their parenting than parents of NBW in observed interactions with their infants/children (Bilgin & Wolke, 2015). Thus, despite ELBW or VLBW infants not being exposed to more childhood risk factors (Lieshout et al. 2018) or poorer parenting (Jaekel, Pluess, et al., 2015) overall, they are more vulnerable to the effects of childhood risk factors on scholastic or depression outcomes. Further evidence is provided by the Poehlmann et al (2015) study that investigated LBW children over the first 6 years and found that less negative parenting, as defined by lower levels of anger and criticism, predicted children's likelihood of resilience across multiple domains of development. However, contrary to a promotive factor interpretation, more positive parenting was not associated with more adaptive outcomes. These findings are consistent with a Diathesis-Stress Model that predicts that those who are vulnerable (e.g. ELBW) do much more poorly in their mental health or achievement compared to those considered not vulnerable when exposed to stressors. In contrast, those who are invulnerable are less affected by childhood risk factors.

ELBW/EPT or VLBW/VP experience many more neonatal risks than those born LBW or late preterm. At what degree of prematurity or LBW may these limits for developmental

plasticity, i.e. the ability to take advantage of protective factors to change developmental trajectories start? Wolke et al. (2015) showed that around 34 week gestation (or around 2000g birth weight) is a turning point in effects of gestation on developmental outcome such as IQ. While below 34 weeks gestation each week lost in gestation was related to an IQ point loss of 2.3 points, there was no significant loss per gestation week (0.3 points per week) between 34-41 weeks gestation. Thus significant vulnerability (at least for IQ) starts at around 34 weeks gestation but does this also indicate reduced developmental plasticity to protective factors? The Infant Health and Development Program (IHDP) (McCormick et al., 2006) is the largest randomized controlled trial of intensive social intervention conducted for LBW children in comparison to a follow-up services group (FUO) only. The LBW were stratified into two groups, those born at birth weight $\leq 2000\text{g}$ and those born at 2001-2500 g. The Intervention group (INT) had weekly home visits in the first year and every other week in year two and three after birth centred on improving parenting. At the end of year 3, they were entered in community education programmes for at least 20 hours per week. Early follow-up while the intervention was ongoing (3 years) or just completed (5 years) showed significant better emotional, behavioural and cognitive development in both birth weight groups in the INT compared to the FUO. However, at 8 and 18 years of age only those born $>2000\text{g}$ at birth still benefitted from the intensive intervention in early childhood (although the effects were reduced), while no positive effect at all was found for those LBW $<2001\text{ g}$ in cognitive, behavioural, emotional or crime outcome. Significant vulnerability for functional deficits increases around 34 weeks gestation (roughly below 2000g birth weight), and developmental plasticity for protective mechanisms seems also to be impaired.

Are these findings consistent with DOHaD as interpreted by van Lieshout et al (2018)? It may not be safe to conclude that ELBW is the result of prenatal exposure when 50% of spontaneous ELBW births are unexplained. Very or extremely low birth weight infants experience many neonatal complications and early neonatal social deprivation such as incubator care and frequent adverse handling that may affect endocrine mechanisms, brain development and long term development. Premature birth occurs at a time when the major organs are immature and neonatal intensive care is provided to support, for example, immature temperature regulation abilities, inability to orally feed (e.g. intravenous) and assisted breathing due to immature lungs. Brain development is rapid during pregnancy and encephalopathy of prematurity is a complex amalgam of maturational and trophic disturbance and superimposed complications (Volpe, 2009), some of which may have started prenatally but many are a result of being born immature and cared for extra-uterine. For example, by term-equivalent age an EPT brain is still smaller and has 40% less cortical folding than one that matured intrauterine to term birth. Anatomical, cholinergic system abnormalities and network changes after VPT/VLBW birth are still present in adulthood and related to functional outcome. Thus it is not surprising that long term effects on adult function have been found to be more strongly related to neonatal treatment and parenting rather than antenatal complications (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2017)

There are some conclusions to be drawn from the limited research on resiliency after preterm birth so far:

1. EPT/ELBW and VP/VLBW are much more vulnerable to further childhood risk factors than term born or NBW.

2. EPT/ELBW and VP/VLBW are less sensitive to protective factors than term born or NBW.
3. Taken together, EPT/ELBW and VP/VLBW require a reduction of adverse neonatal exposure, a much more optimal childhood environment that either removes childhood risk factors or interventions such as highly optimal parenting to reach, on average, functional outcome levels compared to those born at term or normal birth weight.
4. Based on current knowledge, postnatal interventions promise to be more successful if centred on those born late preterm (>33 weeks gestation) or of larger LBW (>2000g) who are less vulnerable and show more developmental plasticity. From a public health perspective, they are not only more amenable to intervention but make up 85% of the population of preterm born.

There are also implications for future research:

1. Large observational studies are necessary to test a comprehensive list of resiliency factors and conduct subgroup analyses (e.g. by sex; according to degree of prematurity) and include prospective measures of the continuum of caretaking casualty already in early childhood such as individual, family, peer social relationship and neighbourhood factors. However, we cannot just wait for these future studies into adulthood. An alternative is to combine VLBW cohort studies such as by Lieshout et al (2018) and others across the world via data sharing for analyses of resiliency factors to adult outcomes. This has its own challenges relating to researchers' willingness to share data, ethical considerations, and appropriate harmonization of data. These challenges are addressed by current collaborative networks

such as RECAP-preterm (<https://recap-preterm.eu/for-scientists/work-packages/>) and APIC (<http://www.apic-preterm.org/>).

2. Intervention studies with EPT/ELBW and VP/VLBW children are necessary at crucial times, (Wolke, 2015) starting in the neonatal unit, at the transition to home and school which are particular challenging for these children and their parents and where further risk factors (e.g. peer bullying but also protection may occur.

3. Experimental studies to understand whether it is prenatal adversity, the immaturity at time of birth, the superimposed neonatal complications or the early stressful social deprivation of ELBW/VLBW children that are associated with their vulnerability to later environment are not possible for good ethical reasons. However, comparative investigations of naturalistic studies comparing those exposed to only antenatal problems (e.g. born small for gestational age), only exposed to extreme early postnatal deprivation and EPT/ELBW and VP/VLBW cohorts may be fruitful to determine causes for limits to resiliency.

We have accumulated a lot of knowledge of the vulnerability associated with prematurity or LBW but we are still in infancy in understanding the limits to developmental plasticity and resiliency after preterm birth. This is surprising, considering that many of these high risk children develop adaptively into adulthood. It is high time to learn from those who did beat the odds. The outlined research programme is likely to provide us with targets for interventions specific for EPT/ELBW and VP/VLBW children and their families.

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