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Long-term consequences of non optimal birth characteristics

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Abstract

The intrauterine milieu, gestational length as well as size at birth have a profound impact on the individual’s mental, physical health and development both in childhood as well as in adult life. Preterm birth and restricted fetal growth are associated with neuro-developmental sequelae, including increased symptoms of psychiatric disorder in childhood and early adulthood. There is also evidence that physical morbidity such as the metabolic syndrome is more common in adult life. In addition, preterm birth and restricted fetal growth have been shown to be related to respiratory disease, infectious disease, and even malignancy. Morbidity, mental and physical as well as personality/intellectual traits have a huge impact on family planning and reproductive performance in adults. As restricted fetal growth may alter organ structure and functions, it is likely to also influence subsequent fertility and/or reproductive health. Our own studies as well as those of others report that individuals with non optimal birth characteristics appears to have a reduction in childbearing and a deviant reproduction pattern compared to controls. Future studies with sophisticated models for measuring the most vulnerable period of birth for children who have a low birth weight or who are at risk for being born preterm are needed to be able to explore the underlying biological mechanisms and also to plan for prevention as well as for interventions during pregnancy.
Introduction

The intrauterine milieu, gestational length as well as size at birth have a profound impact on the individual’s mental, physical health and development both in childhood as well as in adult life. Size at birth is the function of the rate of maternal investment during the pregnancy and length of gestation. The mother supplies oxygen and essential nutrients to the fetus via placental blood flow supply.

Maternal genes have a specific influence over fetal growth. Besides the weight and height of the mother, race, parity, age, energy intake and gestational weight gain play an important role in growth regulation of the fetus. Life-style factors are also of importance; e.g. smoking, drugs and toxic exposure and nutrition. Social status and maternal care provided are also vital for the growth and well being of the fetus.

Intrauterine growth restriction (IUGR) refers to fetal growth that is below that of the genetic potential of the particular fetus. Fetal growth can be measured in several ways; crown-heel length, head circumference, weight height ration, skin fold thickness and ponderal index. The prevalence of IUGR varies in the developed world between 3%-7%. IUGR may be symmetrical or asymmetrical; symmetrical growth restriction, which accounts for 25% of IUGR cases, results in the entire body being proportionally smaller than it otherwise would be. Asymmetrical growth restriction is a more serious form of IUGR and is often due to placental insufficiency in the later part of pregnancy.

Small for Gestational Age (SGA) is defined as a birth weight < -2 SD of the mean weight for the gestational length. Large for Gestational Age (LGA) is similarly defined as a birth weight > +2 SD of the mean weight for the gestational length.1,2

“Moderate preterm birth” is defined as being born between gestational week 32 and 36, and “very preterm birth” as being born before gestational week 32. The prevalence of preterm birth in Europe is between 5.5-11.4 %.3

Low birth weight is mostly categorized in three categories: Low birth weight (LWB ≤ 2500gr), Very Low birth weight (VLBW ≤ 1,500 g), Extreme low birth weight (ELBW; ≤ 1000 g).

In Sweden the incidence for the three different categories are; LWB – 3.5 %, VLBW – 0.2% and ELBW -0.00034 %. The incidence and survival rates vary between different countries.4
The relation between stress and psychiatric illness during pregnancy has been the subject of debate and investigation because psychiatric illness in the mother affects both the mother and the neonate. In spite of the importance of this situation, the complexity of the psychological, physiological and environmental processes involved in mental illness and the supposed negative consequences for the fetus during pregnancy as well as for the child later on in life are only now beginning to be understood.\textsuperscript{5-7} Anxiety disorders (e.g. generalized anxiety, panic disorder, acute stress and post traumatic stress during pregnancy) are known to be risk factors for premature labor, shortened pregnancy length, low-birth weight and adverse perinatal outcomes (e.g. small for gestational age) and for development problems later in life.\textsuperscript{8-14} There is also evidence that an altered hypothalamic-adrenal-pituitary axis (HPA) in women with anxiety during pregnancy can be a result of increased stress.\textsuperscript{15,16}

Lilliecreutze 2011 \textsuperscript{17} condensed the pathways for stress/anxiety from mother to fetus:

1. Neuroendocrine system

The effect of maternal hormones on the uterus and the in-utero exposure of the foetus to abnormally high levels of maternal hormones, especially cortisol are plausible mechanisms by which maternal stress affects the foetus.

During pregnancy, corticotrophin releasing hormone, (CRH) from the placenta is released in an exponentially increasing amount over the course of gestation into maternal and foetal compartments.

CRH from the placenta is stress sensitive and is modulated in a positive, dose-dependent manner by all the major biological effectors of stress, including cortisol, norepinephrine, oxytocin, angiotensin II, both forms of interleukin-1 and hypoxia. Maternal adrenocorticotropic hormone (ACTH) and cortisol stimulate placental CRH secretion which in turn further activates the maternal HPA axis, establishing a positive feedback loop that results in elevated levels of CRH, ACTH and cortisol during the course of gestation.

CRH has a central role in coordinating foetal and maternal endocrine events involved in parturition. An increased level of CRH is therefore associated with the initiation of preterm labour. In addition, elevated maternal cortisol in humans is associated with lowered birth weight and premature birth. There is support in the literature for believing that excess glucocorticoids during development have multiple adverse effects.

The enzyme placental 11\textbeta-hydroxysteroid dehydrogenase (11\textbeta-HSD) type 2 serves as a functional barrier to protect the foetus from excessive exposure to high levels of maternal
cortisol. Reduced placental 11β-HSD2 function has been associated with low relative birth weight and severe foetal distress.

2. Immune/inflammatory system

Stress hormones regulate Th1/Th2 patterns and type1/type2 cytokine secretion and can thereby potentially alter the balance between these two arms of acquired immune responses. Maternal stress can thereby act via an immune/inflammatory pathway by modulating systemic and placental-decidual immunity, resulting in an increased susceptibility to intrauterine and foetal infection and inflammation, known risk factors for preterm birth. Stress could in this way modulate susceptibility to developing maternal genital tract infection during pregnancy and also contribute to a susceptibility to preterm birth in the presence of infection.

3. Cardiovascular system

The activation of the sympathetic nerve system during stress and anxiety results in a decreased uteroplacental perfusion. This might be explained by the fact that cortisol and catecholamines are known to affect vessel tone and could contribute to foetal growth restriction among women experience stress and anxiety during pregnancy.

In the past decades there has been an improvement in the medical treatment of children born preterm or with reduced fetal growth. This has resulted not only in a much higher survival rate of these children, but also in a higher number of surviving children with vulnerability for chronic conditions both mental and physical and as young adults a susceptibility to reproductive difficulty or failure.

**Physical morbidity**

Several studies have proposed a connection between restricted fetal growth and preterm birth and an increased risk for major diseases in later life, including e.g. the metabolic syndrome, which includes diabetes, high blood pressure, obesity, and cardiovascular disease. Different theories aimed at exploring the mechanisms behind these associations have developed and perhaps the most debated of these is Barker’s “the fetal origins of adult disease” hypothesis. The main concept of this theory is that “…an unfavorable development, or insults during fetal life, might induce lifetime effects on the subsequent development of body systems and hence give rise to major disease processes…” Previous research has also established that non-optimal birth characteristics are related to diseases of the nervous system, such as cerebral palsy as well as visual and hearing impairments. The major pathophysiological mechanisms by which these associations occur include intrauterine infections,
central nervous system malformations, and reduced placental function. In addition, preterm birth and restricted fetal growth have been shown to be related to respiratory disease, infectious disease, and even malignancy.

For children born with low birth weight, ELBW and VLBW, there are now long-term follow up studies on clinical material where the children have started their young adult life. Gäddlin and co-workers have followed a consecutive regional cohort of 86 VLBW children since their birth 1987-88 with different measurements at 40 weeks, 4, 9, 15, and 20 years with an equally large group of children born at term serving as controls. The majority of the VLBW children were healthy in early to mid adolescences. There were a few with handicaps that influence their daily life; 6% had cerebral palsy and 6% had been diagnosed with attention deficit hyperactive disorder (ADHD). When the children were 15 years old, their cognitive, academic and behavior functions were assessed. The girls in the VLBW group had fewer problem scores on the behavior test than did boys. But overall the VLBW children performed significantly lower on the cognitive and academic test than their at-term controls and 49% had an IQ lower than 85.

Gäddlin and colleagues have also measured the VLBW children’s own perception of their health and well being and have found that the majority of VLBW subjects were healthy at 20 years of age and managed transition to adulthood in a manner similar to the controls. A minority had handicaps that influenced their physical function. ELBW and severe neonatal complications were associated with poorer self-perceived physical health in early adulthood. VLBW subjects did not differ significantly from their at-term controls in self-perceived health, use of tobacco, education, occupation and way of living. Sixteen of the 77 young adults who participated in the study at the 20 year follow up had cerebral palsy, attention deficit hyperactivity disorder, or isolated mental retardation, and those differed significantly from the controls in physical functioning and physical health score. VLBW subjects were significantly lower in weight and shorter than their at term controls. Vaderhus study from Norway on preterm children (born < 28 gestational weeks and < 1000 gram) found similar results and also found that learning and or attention problems strongly influence the results of the children’s health-related quality of life.

**Psychiatric morbidity and personality**

Preterm birth and restricted fetal growth are associated with neuro-developmental sequelae, including increased symptoms of psychiatric disorder in childhood and early adulthood.

Accumulating evidence indicates an association between being born small for gestational age (SGA) and increased risk of mental illness and psychosocial risk behavior i.e. lower
intelligence, poor academic performance, low social competence and behavioral problems, compared with individuals born appropriate for gestational age (AGA).

Low birth weight has been related to both psychiatric symptoms and psychiatric disorders including eating disorders, schizophrenia, and suicidal behavior.\textsuperscript{33, 37, 38} The personality of those born with restricted fetal growth has recently also gained some attention.

Some studies report that men and women born with very low birth weights display fewer negative emotions and are more cautious in late adolescence and young adulthood as compared to controls.\textsuperscript{24} Others, on the other hand, report a higher risk of internalizing symptoms, attention problems, and relational problems that might influence life in a negative way.\textsuperscript{39, 40}

Preterm birth and/or fetal growth impairment have recently been subjects for research concerning mental illness in childhood, adolescence as well as during the adult part of our life. Low birth weight has been related to both psychiatric symptoms and psychiatric disorders\textsuperscript{39, 41-43}, and in those children born preterm there is some evidence of an increased mental burden.\textsuperscript{44, 45} It has also recently been shown amongst a sample of individuals born preterm and small for gestational age (SGA) that symptoms of anxiety and depression were more frequent.\textsuperscript{46}

The Avon Longitudinal Study of Parents and Children recruited a large prospective cohort of 14,000 pregnant women in Bristol 1990-1991. The aim of the study was to determine the long term effects of antenatal stress or anxiety on the behavioural development of the child. For the 15% mothers with a high anxiety level during pregnancy, Lou and colleagues\textsuperscript{47} have suggested a “foetal stress syndrome” and because of that an assumed impact of adverse antenatal life resulting in a smaller head circumference, lower birth weight and lower neurological scores.

In general SGA works as the ideal marker of foetal growth impairment. However, it is still less well studied than low birth weight. By linking medical birth registries to those of hospitalization further relationships have been shown. Examples of these are relationships between low birth weights or SGA and hospitalization caused by schizophrenia in late adolescence and adulthood; very preterm birth and SGA and hospitalization because of anorexia nervosa; SGA and suicide.\textsuperscript{33, 37, 48} By linking such registries, results have also shown relationships between low birth weight children of 14 years or younger and mental retardation, Asperger ’s Syndrome, learning disorders, and eating disorders among others.\textsuperscript{49}

The evidence of a connection between birth characteristics and psychiatric illness has been of variable strength, depending on the sample size and validity. There seems to be a dose-dependency and also some differences between the sexes. There is evidence that boys and girls show different types of psychiatric problems where boys seem to be more vulnerable to substance-related disorders. Also in
men born preterm, and SGA, there were strongly increased risks for hospitalizations within the following subcategories of: mood disorders; personality disorders; psychotic disorders; child-psychiatric disorders and mental retardation.

In our population-based register-study\textsuperscript{50} we found that males within the study cohort who were born preterm suffered a very modest increased risk of psychiatric hospitalization in late adolescence and early adulthood. In comparison, subgroups of males born SGA and, to a lesser degree also females born SGA, had a higher risk of psychiatric hospitalization, especially males born SGA and preterm. The evidence that those born SGA were at a greater risk was further supported by the fact that SGA males were over-represented within all hospitalization-duration subcategories.

**Fertility and childbearing**

Psychiatric ill health and also personality/intellectual traits as well as socio-economic factors may have a huge impact on family planning and reproductive performance in adults. For adults born preterm, with low weight, or small/large for the gestational birth week there is also the combination of psychiatric ill health and physical morbidity. As restricted fetal growth may also alter organ structure and functions, it is also likely to influence subsequent fertility and/or reproductive health. The “window” or the sensitive period for the fetus that might affect the development and organization of specific tissues and hormones may have effects that persist throughout life.

The individual organ system affected is determined by its unique vulnerability, based on the timing of the exposure or lack of exposure, i.e. the time at birth and the size at birth. Thus development of reproductive organ and hormonal status of a child when being born at a non optimal time therefore might have a profound impact on his or hers reproductive pattern and fertility outcome in adult life.

Our own studies and those of others report that very-low-birth-weight women appear to have a reduction in childbearing compared to controls.\textsuperscript{51,52} Some have also found evidence of restricted fetal growth being related to reduced ovulation rate and smaller internal genitalia.\textsuperscript{53} In short, Ibanez et al. believe that: SGA induces hyperinsulinemic/hyperleptinemic insulin resistance (thrifty fenotype / fetal programming models) and stunted growth (height, genitalia – male and female), early puberty, low ovulation rates, and possibly reduced reproductive rate.\textsuperscript{53}

Some studies have reported an impaired gonadal function in males born SGA. For boys born with restricted fetal growth there are reports of elevated serum levels of estradiol, dihydrotestosteron and inhibin B. The authors speculated that fetal growth restriction can lead to permanent disturbances in the steroid biosynthesis.\textsuperscript{54,55} Cicognani and co workers found that SGA boys compared to AGA boys have
pituitary-gonadal axis function that tend toward hypogonadism. SGA boys with smaller testes had lower final height relative to target height and for the SGA boys, inhibin B correlated with testicular size. The authors concluded that there is a disruption of the exocrine function in subjects with smaller testicular size who failed to show a complete height catch-up growth. This study supports a link between low birth weight and lower fertility in adult males. Also differences in personality and/or behavior and the ability to form relationships may be involved in explaining the reduced childbearing among women and men with restricted fetal growth. The relation between adolescent morbidity and future fertility has only sparsely been addressed, although adolescence is a complex period during human growth. Previous studies suggest a reduction in childbearing following several kinds of morbidity during childhood. Psychosocial factors may influence the relation between adolescent morbidity and later childbearing. Adolescent-onset psychiatric disorders seem to be associated with increased probability of teenage pregnancy. Most previous studies have studied the effect of specific diagnoses or conditions on future fertility or childbearing and the focus has mainly been on childhood morbidity.

We had previously reported that non-optimal birth-characteristics such as being born (SGA) or preterm are connected not only to higher risks of adolescent hospitalisations but also to later childbearing. In the Ekholm Selling study women hospitalized due to genitourinary diseases, respiratory diseases, abdominal problems, and abuse of alcohol and drugs were more likely to have given birth then women without these diagnoses. Not surprisingly, hospitalizations due to cerebral palsy and congenital malformations tended to decrease the ability to bear children. Women hospitalized due to psychiatric diseases had an increased likelihood of giving birth at 20-24 years but a reduced likelihood hereafter. To determine if this is an effect that will last for the reproductive life of the cohort merits further investigations. Data on boys/men with psychiatric morbidity and their reproduction and fertility are sparser and this group is harder to investigate through population registers but improvements are being made.

In the Ekholm Selling study of girls born with non-optimal birth characteristics, we found that girls born SGA had a hazard ratio of giving birth during the study period 25% lower among women who themselves were born with very low birth weights, compared to women who weighed ≥ 1.500 g at birth. Adjusting for childhood socio-economic characteristics did not markedly change the results. Ekholm Selling also found that women who were twins were less likely to have given birth. On the
other hand, women who were born SGA were 9% more likely to have given birth during the study period. The explanation for this might be due to personality and temperament characteristics as well as to earlier pubertal development.\textsuperscript{59}

There is also evidence for an intergenerational effect of non optimal birth characteristic. In our register study of 38,720 mother-offspring pairs, preterm birth appears to be more common in children whose mothers are born preterm or SGA, compared to mothers born at term. Also mothers whose fetal growth was moderately reduced but who did not meet the criterion of being born SGA are at higher risk of giving birth to both preterm and SGA children.\textsuperscript{60} Swamy et al. found in the Norwegian cohort from 1957-1988 that the incidence for girls born preterm of having a preterm offspring was 14% compared to 6.4% in girls born at term. This pattern could not be seen in men born preterm.\textsuperscript{61}

Long term follow up studies on fertility outcomes for individuals born with one or more non optimal birth characteristics are time dependent, i.e. the reproductive period for most women is the time between 20 and 40 years of age whereas for men the possibility for fertilization is considered to be life long although with a decline in old age. Today we can offer persons with fertility problems a variety of assisted reproduction treatments such as IVF, gamete donation, etc. Men and women born with non optimal birth characteristic may be in greater need of these treatments in order to have children. Thus, we found a higher incidence of preterm birth in a consecutive clinical sample of 2000 men and women born in Sweden who had sought infertility treatment (unpublished data). Follow up on treatment regimes for the group who themselves are born non optimal is needed in able to study outcomes and the effects of treatment.

**Conclusion**

Alteration in susceptibility to diseases in childhood and later in adulthood of those born with one or more non-optimal birth characteristics may be related to impaired development in the uterus. Therefore, understanding the mechanisms which cause low birth weight is important for the development of future interventions for pregnant women and neonates. This could give these children a better chance of a healthy life both in the immediate future and in the long term and may also improve the possibility for them to have children in the future.

Future studies with longer follow up and with sophisticated models for measuring the most vulnerable period of birth for children who have a low birth weight or who are at risk for
being born preterm are needed to be able to explore the underlying biological mechanisms and also to plan for prevention as well as for interventions during pregnancy.
References


