2.2   Developmental origins of health and disease

Do and how do health and disease originate in early life? A new area of research that aims at illuminating the developmental origins of health and disease (DOHaD) has emerged and led to the foundation of the DOHaD society with its first international conference held in 2003. Within this society, the majority of the research activities focuses on the intrauterine stage of development and tries to find out more about relevant intrauterine exposures, their consequences on fetal and child development and health, and the biological mechanisms involved in linking the intrauterine environment and long-term outcomes.

2.2.1 Historical perspective on 'developmental origins of health and disease' research

Initially, work on the developmental origins of health and disease focused on the relationship between birth weight, which was regarded as an indicator of intrauterine conditions, particularly nutrition, and adult health. David Barker and colleagues from Southampton pioneered the human research in this field. Based on observational studies, in the 1980s, they put forward the 'fetal origins of adult disease hypothesis', stating that "undernutrition *in utero* permanently changes the body's structure, physiology, and metabolism, and leads to coronary heart disease and stroke in adult life" (Barker, 1998, p. 13). This hypothesis emerged from early observations of a strong relationship between rates of coronary heart disease and respiratory cancer occurring in the 1960s and 1970s and infant mortality rates at the beginning of the century in Norway, England, Wales, and the United States (Barker & Osmond, 1986; Buck & Simpson, 1982; Forsdahl, 1977). The researchers concluded from these relationships that early life factors are linked to the risk of disease in adult life. In 1985, Wadsworth and colleagues reported an inverse correlation between adult blood pressure and birth weight in men and women born in 1946 (Wadsworth et al., 1985). Similarly, tracing more than 5000 men born between 1911 and 1930 in Hertfordshire, England, Barker and coworkers observed that men with the lowest weights at birth and at one year of age had the highest rates of death from ischaemic heart disease (Barker et al., 1989).

Comprehensive epidemiological research worldwide has extended these initial observations, showing that low birth weight is linked to an increased risk of morbidity, including cardiovascular and metabolic diseases, and premature mortality (Barker et al., 1993; Forsen et al., 2000; Frankel et al., 1996; Hoy et al., 1998; Martyn et al., 1998; Osmond et al., 1993; Stein et al., 1996). For example, based on review of 103 studies, it was estimated that a 1 kg higher birth weight is typically associated with a 0.6 to 1.9 mm Hg lower systolic blood pressure (Huxley et al., 2002).

In the meantime, research on the fetal origins of health and disease has expanded. For example, in addition to prenatal growth, the role of postnatal growth has come into focus. It has become clear that weight gain within the first years of life renders those with low birth weight particularly susceptible to coronary heart disease (Barker et al., 2005). Therefore, the concept that was originally termed 'fetal origins of adult disease hypothesis' has been renamed 'developmental origins of adult disease hypothesis' (Barker, 2004). Moreover, exposures other than nutrition, for example medication and stress during pregnancy (see below), have received considerable attention. Only relatively little work has focused on the short-term effects of intrauterine adversities on health during childhood.

2.2.2 Intrauterine programming

In the discussion on the developmental origins of health and disease, a number of theoretical concepts have been introduced to explain the process underlying the observed associations between birth weight and health (McMillen & Robinson, 2005). However, it is fair to point out that a precise, generally accepted definition of this process is still lacking. Even a recent glossary established to define key concepts used in the field of the developmental origins of health and disease fails to offer thorough definitions (Barker, 2004). Perhaps the most widely accepted and used concept is 'programming', which describes the process by which a stimulus or insult at a critical stage of development has lasting or lifelong significance (Lucas, 1991)[2]. This definition unifies core ideas, including the lasting changes in the organism and the critical period during which perturbations must occur to have maximal effect, which are also found in other concepts, for example the 'thrifty phenotype hypothesis'[3], and 'developmental plasticity'[4]. It was in a landmark investigation more than 40 years ago, when Widdowson and McCance (1963) demonstrated the existence of such critical periods, thus taking up the concept of 'imprinting' which had been rediscovered and popularized by

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[2] Focusing on different aspects of this process, including the cause, target tissue, outcome, timing or assumed underlying mechanism, different specifications such as 'nutritional programming' (Bagby, 2007), 'endocrine programming' (Fowden et al., 2005), 'behavioral programming' (Sousa et al., 2008), 'perinatal programming' (Ingelfinger & Woods, 2002), 'developmental' and 'biological' programming (Rutter & O'Connor, 2004), or 'epigenetic programming' (Darnaudery & Maccari, 2008; McGowan et al., 2008; Weaver et al., 2004) have been introduced.

[3] In 1992, Hales and Barker introduced the 'thrifty phenotype hypothesis' (Hales & Barker, 1992), proposing that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces a 'thrifty' fetus with permanent changes in glucose-insulin metabolism.

[4] The term 'developmental plasticity' proposes that a given genotype can give rise to different phenotypes, depending on environmental conditions. This concept takes on an evolutionary perspective and understands fetal responses to the intrauterine environment as 'adaptive' responses, which prepare the individual for the type of extrauterine environment into which he or she is likely to be born (Bateson et al., 2004). The fetal responses are likely appropriate in the short run and they may also be adequate in the long run provided that the anticipated postnatal environment is comparable to the prenatal one. Only if the postnatal environment is not as has been anticipated, the adaptive changes might be disadvantageous in the long run.

Konrad Lorenz, who demonstrated how geese would imprint on the first moving stimulus they saw within a critical period shortly after hatching (Krebs & Sjolander, 1992). Widdowson and McCance discovered that undernourishment of rat pups only during the three weeks of lactation but not at a later stage of development resulted in a lifelong slower weight gain as compared to well-nourished controls, even though the deprived rats had access to *ad libitum* diets after deprivation in both conditions.

In sum, several overlapping and loosely defined concepts try to describe the simple fact that early experiences have long-lasting effects. To describe this association, in this thesis, the term 'programming' is used, and its definition from Lucas (1991) applies.

2.3   Fetal development

To better understand the intrauterine processes with which early factors can interfere, this section provides a brief overview of general principles of human embryology and critical periods of organ development. As the presentation of a comprehensive picture of the current knowledge about intrauterine organ development would go beyond the scope of this work, further reading is recommended below.

In brief, after the implantation of the blastocyst in the endometrium of the uterus, three germ layers form during the third week of development[5], the embryonic ectoderm, mesoderm and endoderm, which are the precursors of all tissues and organ systems to develop (Sadler & Langman, 2006). Each organ primarily originates from the pluripotent cells of one of these germ layers, even though the other germ layers also contribute to its development (Schulze, 2006). The ectoderm gives rise to the nervous system, sensory organs, the skin with its appendages and the pituitary gland. The mesoderm gives rise to the musculoskeletal, urogenital and cardiovascular systems. The endoderm gives rise to the gastrointestinal and respiratory system.

Human intrauterine development can be divided into two major stages, the embryonic and fetal period, which differ with regard to their primary functions and, as a consequence, the organism's susceptibility to adverse exposures in the intrauterine environment that occur in the respective period (Gilbert-Barness & Debich-Spicer, 2004; Moore & Persaud, 2003). The embryonic period is primarily characterized by organogenesis and stretches from fertilization to the end of the eighth week of gestation, by which time the beginnings of all major

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[5] In general, the length of pregnancy is considered to be 280 days or 40 weeks after the onset of the last normal menstrual period (LNMP), or, more accurately, 266 days or 38 weeks after fertilization (Sadler & Langman, 2006). For the purpose of illustrating embryonic and fetal development, in this section, embryonic/fetal age is calculated from the time of fertilization, as is common practice in embryology. In all other sections of the thesis, gestational age/length of gestation is expressed according to the onset of the LNMP, as is common practice in obstetrics and gynecology.

structures are present and the embryo has a remarkably human appearance (Gilbert-Barness & Debich-Spicer, 2004). The following fetal period lasts until full term and is primarily a period of growth and maturation. The rate of head growth is highest in the first trimester. During the fourth and fifth months, the fetus lengthens rapidly. Weight increases by approximately 50% of the term weight in the last 2.5 months of intrauterine life (Sadler & Langman, 2006). For illustrative purpose, Figure 2.1 presents growth charts for head circumference, body length, and body weight in the last trimester.
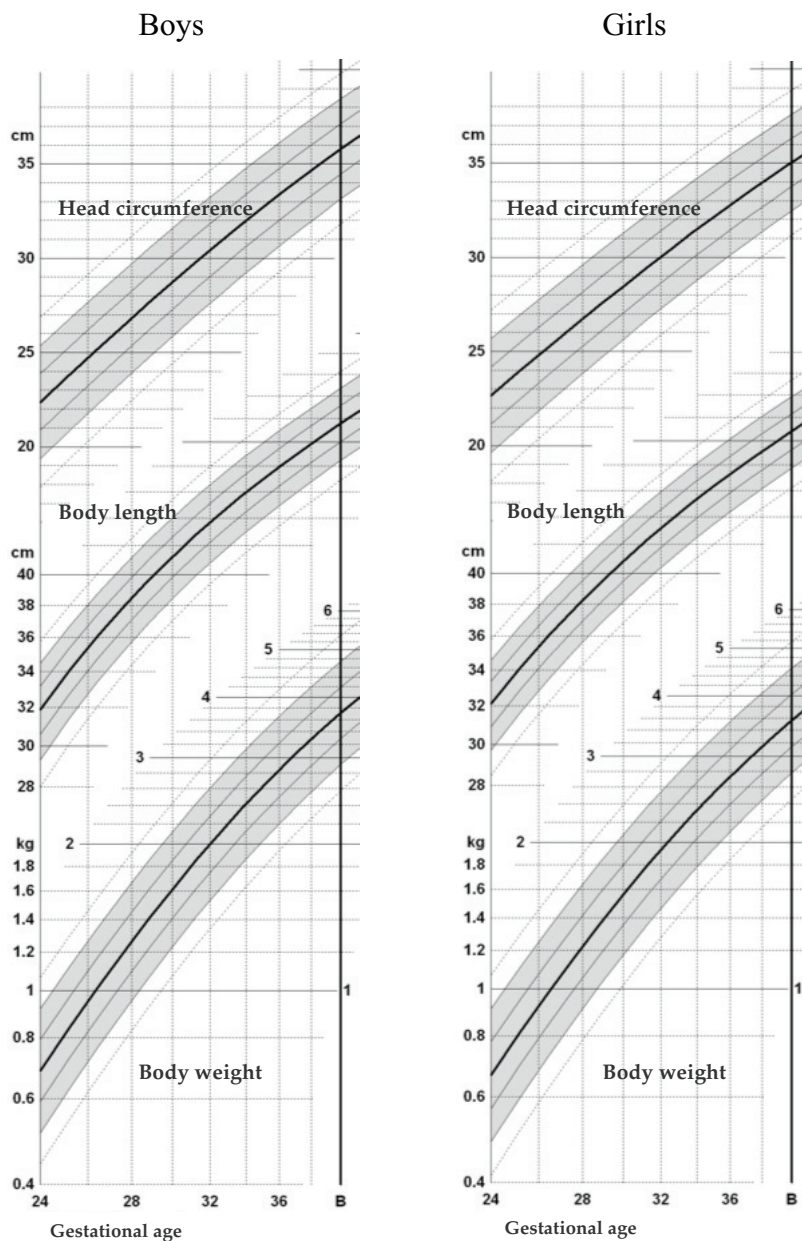

Figure 2.1: Swedish growth charts for head circumference, body length, and body weight from 24th week of gestation to birth (B) for boys and girls. The mean (plotted along bold curve) and the standard deviation (SD; +/- 1SD, +/- 2SD, +/- 3SD) are presented for head circumference, body length and body weight for each age. In a normal population, values of 67% of the children lie between +/- 1SD and of 95% between +/- 2SD (grey shaded area; Figure is reproduced and adapted, with permission, from Niklasson et al., 2008. Copyright 2008 by BioMed Central.

Precursors of many organ systems, including the cardiovascular, central nervous, visual, auditory and immune system, differentiate around the 3rd week of gestation (Moore & Persaud, 2003).

Many factors are likely to underlie deranged organ development, including genetic makeup and an adverse intrauterine environment (Olson, 2006; Rees et al., 2008; Rice & Barone, 2000). Each organ system has a specific critical period in which it is most susceptible to intrauterine perturbations, namely when its cells divide most rapidly. This is generally true for the period of organogenesis and, thus, particularly during weeks 3 to 8, intrauterine perturbations are most likely to result in severe organ malformations (Sadler, 2000; Wilson, 1973). Minor morphological changes and functional disturbances originate in the fetal period (Sadler, 2000; Figure 2.2). For example, in the human fetus, glomerular number increases rapidly during midgestation, after which time no more glomeruli are formed (Gasser et al., 1993). The period of rapid increase in glomerulus number is important in determining the total glomerular endowment. Indeed, maternal undernutrition in midgestation has been associated with an increased risk of microalbuminuria in the adult human offspring (Painter et al., 2005). Interestingly, perturbations in the intrauterine environment within the first two weeks of gestation may interfere with blastogenesis, that is the rapid division of non-specific cells and implantation of the blastocyst, and result in abortion rather than organ malformation (Schulze, 2006).
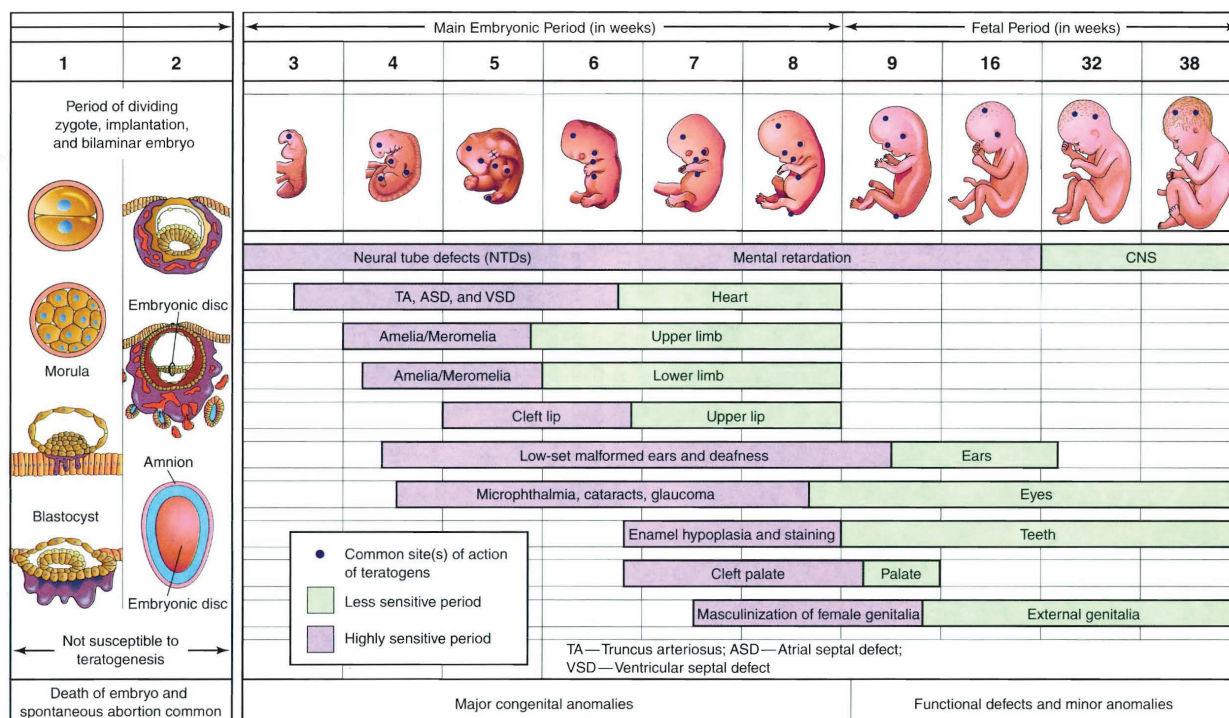

Figure 2.2:   Critical periods of embryonic and fetal development. During the embryonic period, exposures can result in major congenital anomalies. During fetal life, exposures rather lead to functional deficits and minor anomalies (Figure is reproduced, with permission, from Moore & Persaud, 2003. Copyright 2003 by Elsevier).

For a comprehensive overview on basic embryology, the interested reader is referred to the works of Moore and colleagues (2003) and Sadler (2006). More detailed information on morphogenesis and its genetic and molecular regulation in specific organ systems is available in recent, more focused works on the development of the cardiovascular system (Buckingham et al., 2005; Srivastava, 2006), central nervous system (de Graaf-Peters & Hadders-Algra, 2006; Guerrini et al., 2008), endocrine system (Sadler, 2000), immune system (Holt & Jones, 2000), respiratory system (Burri, 1984), digestive system (Rubin, 2007), eye (Barishak, 2001), and ear (Sohmer & Freeman, 1995). The intrauterine development of the hypothalamic-pituitary-adrenal (hpa) axis is presented in detail in chapter 6.

2.4   Maternal-fetal psychobiological programming model

A model of maternal-fetal psychobiological programming shall serve as a theoretical framework integrating the empirical work of this thesis (Figure 2.3). The model consists of three major levels, i) the offspring (embryo/fetus; in the following collectively referred to as fetus), ii) the mother, and iii) the environment in which mother and fetus are living, and two main interfaces, a) the environment-mother interface, and b) the mother-fetus interface (the placenta). Fetal exposures may originate from the environment or the mother. They may either be directly or indirectly (through secondary alterations elicited in the mother and/or the placenta) transmitted to the fetus, where they reach their potential targets and may exert long-term effects. For example, synthetic glucocorticoids that enter the maternal circulation, via injection, easily cross the placental barrier (Brown et al., 1996). By contrast, in order to reach the fetus, psychosocial stress perceived by the mother needs to be translated into a biological signal, for instance an increase in the concentration of cortisol that then passes the potent albeit incomplete placental barrier against endogenous glucocorticoids (Benediktsson et al., 1997). Drawing on the analogy from cell biology, the secondary alterations elicited in the mother and/or placenta are termed 'second messengers'[6].

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[6] The binding of ligands to many cell-surface receptors leads to a short-lived increase (or decrease) in the concentration of the intracellular signalling molecules termed ‚second messengers'. The elevated intracellular concentration of one or more second messengers following hormone binding triggers a rapid alteration in the activity of one or more enzymes or non-enzymatic proteins (Lodish et al., 2000).
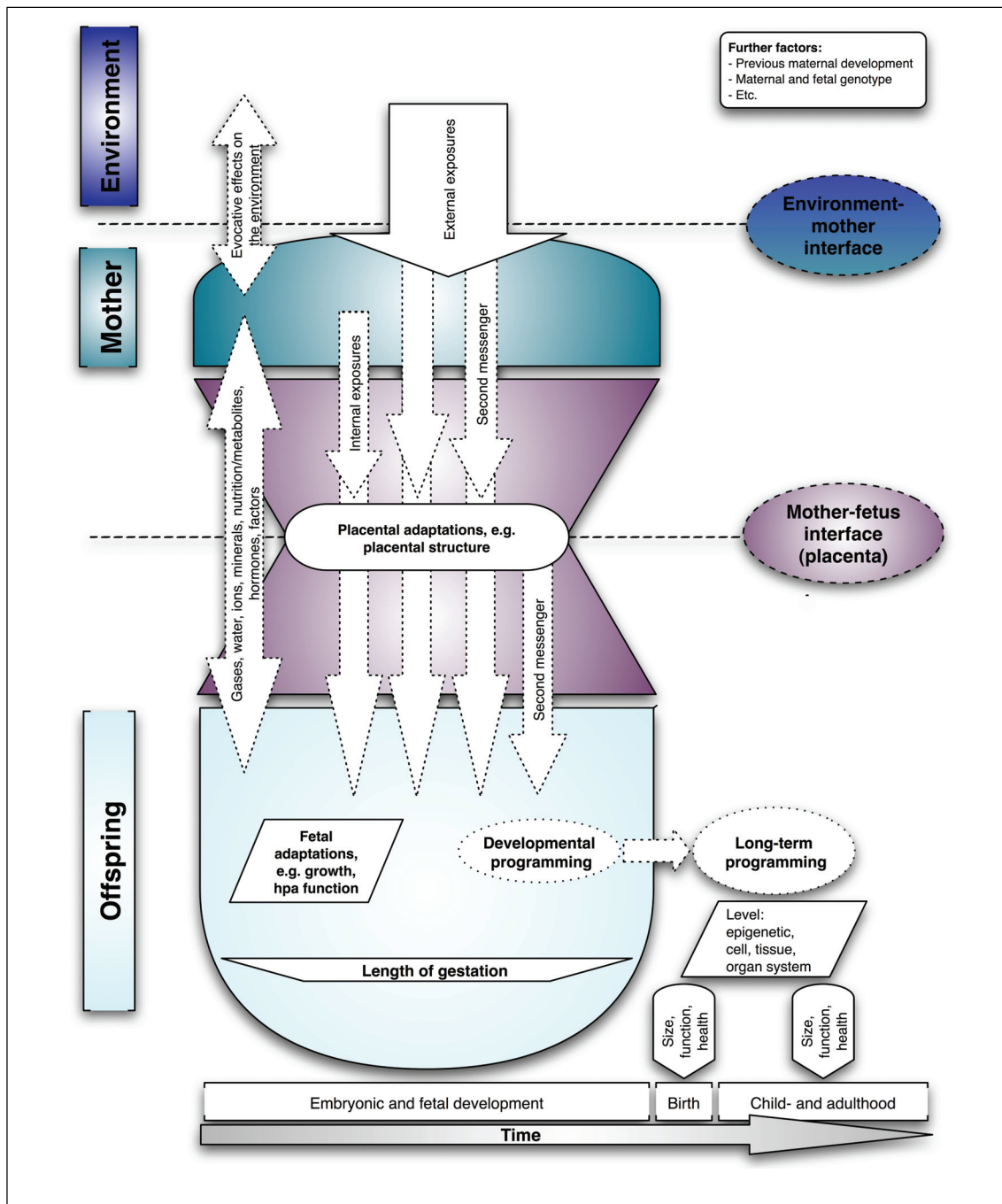
Figure 2.3:   Maternal-fetal psychobiological programming model. The model consists of three major levels, the offspring (embryo, fetus), the mother, and the environment in which mother and fetus are living, and two interfaces, the environment-mother interface, and the mother-fetus interface (the placenta). Fetal exposures may originate from the environment or the mother. They may either be directly or indirectly (through secondary alterations elicited in the mother and/or the placenta) transmitted to the fetus, where they reach their potential targets and may exert long-term effects. Drawing on the analogy from cell biology, the secondary alterations elicited in the mother and/or placenta are termed 'second messengers'.

hpa function = hypothalamic-pituitary-adrenal function