Chapter 2
Calibrating the Next Generation: Mothers, Early Life Experiences, and Reproductive Development

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Introduction

In the spirit of illuminating the invisible, this chapter examines how early life experiences shape a biological sensitivity to context. The priming of growth, development, and adult physiology through early life experiences, also known as biological embedding, is an exciting new area of research that lends itself to integrated systems thinking. Indeed, this body of research demands an integration of social inequality, ecological theory, and the cellular unfolding of development from conception to old age. Or, what Thayer and Kuzawa (2011: 2) call a "promising new convergence of molecular biology, social science, and public health practice." This integrative perspective offers a means to draw on the predictive power of evolutionary theory with the broader strengths of what Anthropologists do best, documenting the circumstances of daily lives in nuanced and detailed ways. By starting from the position that biology, culture, and lived experience are inseparable, we have the opportunity to link real world contingencies of inequality to global patterns of population health.

While signals of environmental quality drive many developmental pathways, the focus of this chapter will be the development of the reproductive system. The chapter begins with a broad overview of early life programming, a brief introduction to the array of early life signals that guide reproductive development including the importance of the timing of these signals, and proceeds with examples of ways to make such invisible signals more transparent in research. As such, this chapter draws on the biological embedding of early life experiences as a means to make sense of the way evolution has shaped gonadal sensitivity to intergenerational, individual, and

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environmental cues about the past, current condition, and future. Many thoughtful scholars have written extensively about elements of this topic (see for example Ellis 2004; Ellison 2003a, b; Jasienska 2012; Kuzawa 2007; Vitzthum 2008), and this chapter will pull some of their ideas together to create a picture of how stressful and low resource environments shape developmental pathways of human reproduction.

Biological Embedding of Environments

From the early studies of high altitude adaptations (Baker and Little 1976; Beall 2007) and the notable contributions of Lasker (1969) on plasticity, biological anthropologists have long been interested in how the environment shapes phenotypes. Early research designs imagined the possibility of disentangling gene × environment interactions by focusing on powerful isolated environmental stressors, such as high altitude hypoxia. However, even in these earliest models, the complexities of disentangling context and biology were obvious (Baker and Little 1976; Little and Haas 1989). Important hypoxia modifications incurred during growth and development argued for at the very least a gene × environment × development model. Fast forward to the new insights of the epigenetics revolution (Carey 2012) and the task of understanding how environmental experiences are embedded in human biology becomes an even more compelling task. Indeed, we now understand that environmental cues—typically delivered via nutrients and hormones—are necessary for the genetic expression of many traits (Jablonka and Lamb 2005). These cues include signals that regulate a host of biological systems (Kuzawa and Bragg 2012), with some deriving from a mother's appraisal of her environmental circumstances passed to her fetus in utero (Bateson et al. 2004; Gluckman and Hanson 2004), and other signals received at critical set points in postnatal life. As our understanding of epigenetics unfolds, the task of making sense of how environments, broadly defined, shape biology across the lifespan creates rich opportunities for human biologists trained at the intersections of evolutionary biology and health.

Environmental information weaves its way into the circuitry and infrastructure of developing organisms through epigenetics and hormonal signals (Shonkoff 2012; Meaney 2010). At the molecular level, environmental information can modify DNA signals by silencing or switching developmental pathways on or off (Meaney 2010). As Charney (2012) suggests, genes do not self-activate nor is every gene transcribed, instead they are turned on or off by the epigenetic regulatory system. The epigenome allows transcription of the DNA to occur in a way that can silence or activate genes without modifying the DNA (Carey 2012). The silencing or activation of genes can be stable across the life course for some genes (e.g., those that occur during embryogenesis), but other genes can be responsive to environmental input at any point in the life span (Carey 2012). Hormonal signals and nutrients may trigger epigenetic modifications that shift developmental pathways, as in the well-documented case of bisphenol A (BPA) and the positive offspring outcomes

when Agouti mouse dams were fed diets rich in methyl groups and long-term negative outcomes of offspring whose dams received a regular diet (Dolinoy et al. 2007). A better sense of the array of signals that can trigger epigenetic modifications is emerging, with much to learn (Meaney 2010).

At the systemic level, the stress–response system (SRS) appears to be a key candidate for facilitating the biological instantiation of local ecology (Hertzman and Boyce 2010; Schulkin et al. 2005; Seckl and Holmes 2007; Reynolds 2013 for an excellent review). Indeed, the SRS appears to help coordinate many of the earliest developmental switch points (Crespi and Denver 2005; Reynolds 2013). A robust body of literature links maternal prenatal stress to perinatal outcomes including infant stress reactivity (Gunnar and Quevado 2007; Lupien et al. 2009; Wadhwa 2005). During pregnancy, the maternal hypothalamic–pituitary–adrenal (HPA) axis ramps up cortisol production three fold over the course of infancy. This cortisol increase helps coordinate a host of systems, not the least of which includes nutrient transport across the placenta to the fetus (Belkacemi et al. 2010). The fetus is only partially protected from the increased maternal glucocorticoids by the placental hormone 11-β-hydroxysteroid dehydrogenase 2 (11βHSD2) which converts glucocorticoids to deactivated cortisone (Harris and Seckl 2010; Seckl and Holmes 2007). Despite mechanisms to buffer the fetus from maternal glucocorticoids, elevated maternal cortisol, whether from maternal stress or undernutrition, represents a signal of environmental stress and appears to increase fetal HPA axis sensitivity (Nyberg 2013). This sensitivity can persist or be recalibrated during the birthing process, early perinatal life, or—some evidence suggests—again during puberty.

During birth and the first days of life, the perinate must establish an autonomous HPA axis. This transition, a developmental switch point (West-Eberhard 2003), creates ample opportunity to receive information about this new postnatal environment. Evidence for increased sensitivity to these signals exists, with higher glucocorticoid receptor density in the gut (compared to postweaning age) but also in the brain, suggesting patterns of caretaking (Gunnar 1998; Gunnar and Donzella 2002; Gunnar and Quevedo 2007) and maternal glucocorticoids delivered via breast milk are critically important to early infant development (Glynn et al. 2007; Hinde 2013; Nyberg 2013). Moreover, these signals, still strongly linked to maternal cues, include "lactational programming" (Hinde 2013; Pike and Milligan 2010) with information about maternal energy stores via leptin (Kiess et al. 1998; Miralles et al. 2006; Smith-Kirwin et al. 1998; Vickers and Sloboda 2012), maternal pathogen experience, and even melatonin in evening breast milk (Hamosh 2001; Illnerova et al. 1993). Glucocorticoids, thus, serve as mediators of metabolic pathways but also the target systems for programming (Reynolds 2013), up-regulating or down-regulating stress reactivity (Gunnar and Quevedo 2007) depending upon the cues being received. In sum, this regulation appears to be a part of the process that allows preferential allocation of resources to important systems but channels resources in thriftier ways if the signals suggest resources are scarce or the environment is risky.

Kuzawa (2007) and others (Ellison 1994; Ellison and Jasienska 2007) draw on life history theory to suggest that the early biological responses of offspring to maternal condition allow organisms to scale metabolism via growth and development for survival and later reproductive investment. Such scaling, according to Kuzawa (2007), in theory allows for a filtering of transient nutritional messages so that investment in reproduction does not outstrip metabolic resources. What then are the broad strokes of how maternal signals can prime early life development down thriftier pathways? Pioneered by Hales and Barker (2001), the thrifty phenotype hypothesis set the stage for reexamining the links between maternal nutrition and fetal growth outcomes. This now well-described hypothesis links the fetal response to signals of prenatal undernutrition with circulatory shifts favoring critical organs that can result in compromised growth for other organs. For adults, the constraints associated with small size at birth, and the catch-up growth that often accompanies growth restriction, are quite noteworthy, particularly in women, although men also experience important consequences (Kuzawa et al. 2010). While the implications of this thriftier metabolism for chronic disease have been a point of interest for theoretical and for practical reasons, a growing body of literature also links these early life experiences to cognitive (Braun et al. 2013; Wadhwa et al. 2009), immune system (McDade 2003), and reproductive (Ellison and Jasienska 2007; Gluckman and Beedle 2007; Jasienska et al. 2006a, b) development.

How Does Biological Embedding Influence Reproductive Development?

In recent studies, associations have emerged linking alterations in the methylation of genes associated with variation in cortisol levels with tissue-specific responses to cortisol for adults who experienced early life growth restriction (Reynolds 2013). These associations make it clear that molecular and system-wide facultative adaptations occur in response to adverse early environments. While less is known about these early life influences on the developing reproductive system than is known for cardiometabolic health, a complex picture is slowly emerging (see Sloboda et al. 2007 for an excellent review). Small size at birth, as a proxy for fetal growth restriction, has been associated with a smaller uterus and ovaries (Hart et al. 2009; Ibáñez et al. 2000, 2002, 2003), higher concentrations of follicle-stimulating hormone (FSH) at 18 years (Ibáñez et al. 2003), and fewer primordial follicles compared to non-growth restricted girls (de Bruin et al. 1998, 2001). Moreover, fetal growth restriction also appears to influence the timing of puberty (Adair 2001; Gluckman and Beedle 2007; Gluckman and Hanson 2006), age at menopause (Elias et al. 2003), ovarian function (Elias et al. 2005; Jasienska et al. 2006b), and a strong association with giving birth to smaller infants, indicating an intergenerational consequence (Aiken and Ozanne 2014; Schulz 2010). Indeed, animal models have shown that even when nutritional conditions improve in the second generation,

including adequate maternal nutrition, smaller size at birth takes several generations to disappear from the matriline (Drake and Walker 2004; Kuzawa 2007). While some of this suite of consequences may be due, in part, to the experience of constraint during fetal gonadal development, there is some evidence for epigenetic mechanisms acting in concert with mechanical constraint (Drake and Walker 2004; Roseboom et al. 2006). Taken as a whole, these data offer intriguing insights into the links between fetal growth restriction and partitioning resources toward reproductive development.

The relationship between the intrauterine growth experience and early postnatal growth and development is critical for understanding how reproductive development unfolds. For example, rapid weight gain in infancy for babies born thin is associated with higher adiposity at age 5 years (Ong et al. 2007), and this in turn influences the timing of reproductive maturation (Cooper et al. 1996; He and Karlberg 2001; Karlberg 2002; Ong et al. 2007; Sloboda et al. 2007). There are two points here as follows: (a) rapid fat gain in infancy irrespective of size at birth appears to influence endocrine systems that drive reproductive development and (b) fetal growth restriction appears to be accompanied by accelerated growth and fat deposition whenever postnatal energetic resources are sufficient to make this possible (Cameron and Demerath 2002; Cameron 2007; Cameron et al. 2011). These patterns of faster growth and early adiposity are strongly associated with earlier age at puberty in longitudinal studies (Adair 2001; He and Karlberg 2001; Kaplowitz 2008). Patterns of postnatal growth are driven, in part, by energetic signals (e.g., leptin in breast milk, insulin), but also through neuronal mechanisms that sense the availability of glucose in real time (Roland and Moenter 2011). Signals of adequate energetic resources ramp up growth patterns and appear to encourage an abdominal pattern of fat deposition (see Yajnik et al. 2003).

Based on the complexities of how patterns of prenatal and postnatal growth interact with fat deposition and endocrine regulation, Wagner et al. (2012) revitalized the concept of the gonadostat. The gonadostat theory (Bhanot and Wilkinson 1983), simply stated, suggests that the decline in hypothalamic–pituitary sensitivity to the negative feedback of gonadal steroids drives the initiation of puberty. This "gonadostat" setting, which begins during fetal life in response to HPA and hypothalamic–pituitary–gonadal axis (HPG) signals, appears to be able to recalibrate during early growth and development. While Wagner et al. focus exclusively on how early life overweight and obesity interact with potential gonadostat settings, the concept can be modified as a means to make sense of the sensitivity of the HPG axis to early life cues. Ellison's (1990, 1994, 1996, 2003b) work has been central in making a case for ovarian sensitivity to maternal condition and here I am blending his work with that of Wagner's et al. to suggest that HPG axis sensitivity emerges early in life, responds to signals of the environment in the early years of life including cross talk with the HPA axis (Ellis 2004), and this in turn acts in concert with other mechanisms to drive the timing/tempo of maturation.

During early postnatal life, the hypothalamus transitions to a more active state with a rise in the release of gonadotrophin releasing hormone (GnRH) and luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. This activation stimulates ovarian follicle activity that then subsides again during early and middle childhood. While the precise regulatory mechanisms that guide the onset of puberty are not well understood, neuropeptides from the kisspeptin family and the GPR54 receptor appear to play important permissive roles as do metabolic signals of energy homeostasis such as insulin, leptin, ghrelin, and neuropeptide Y (Kiess et al. 1998; Roa et al. 2008) among others (Wagner et al. 2012).

Once reproductive maturation occurs, a host of mechanisms that balance maternal condition against the energetic cost of reproduction are well documented (see Ellison 1994, 2003a; Jasienska 2012; Vitzthum 2008). Indeed, ovarian sensitivity to ecological settings was first proposed by Ellison (1994) as a key life history trade-off that balances survival versus reproductive success in poor nutritional circumstances. More recently, Jasienska et al. (2006a) found that this ovarian sensitivity appears to be more responsive/reactive if prenatal growth was restricted. It is also well established that early developmental experiences associated with low energetic resources shape adult hormone profiles, with individuals who experience nutritional constraint during early life having lower peak progesterone (Ellison 1990; Vitzthum 2008, 2009) and estradiol (Jasienska et al. 2006b) when compared to higher resources settings. While critical links remain to be identified in how these lower hormonal profiles influence conception (Jasienska 2012; Vitzthum 2008), the bulk of evidence indicates a dampening of reproductive hormone signaling when women are in marginal condition. Interestingly, recent evidence suggests that energetic resources can be detected in real time via GnRH neurons that sense glucose (Roland and Moenter 2011) to modify HPG settings over the short and longer term. Greater ovarian/HPG sensitivity to energetic homeostasis for women who experienced growth restriction in utero suggests an interesting set of new questions about partitioning of resources and life history trade-offs (Jasienska 2012).

Finally, the relationship between early growth trajectories and the timing of menopause remains poorly understood (Cresswell et al. 1997; Sloboda et al. 2011). There is some evidence to suggest that fetal growth restriction reduces follicle production and increases the rate of follicular atresia (Broekmans et al. 2007, 2009; Hardy and Kuh 2002), indicating an indirect association with fecundity and age at menopause. While much work remains to be done in this area, the current working model for the influence of early life experiences on menopause is that it appears to modify the number and quality of oocytes and interacts with life experiences (e.g., smoking, marital status, and education) to shorten the age at menopause (Murphy et al. 2013; Sievert 2006; Sloboda et al. 2011).

Promising Ways to Reveal the Invisibility of Biological Embedding and Reproductive Sensitivity

The complicated interaction of genes × epigenome × development × environment makes it hard to disentangle causal pathways that allow us to link context to biological experiences. Yet, this task is precisely the task at hand. A number of tried and true approaches are being utilized such as large cohort studies and animal model studies that closely examine proposed mechanisms (e.g., Gardner et al. 2009; Langley-Evans 2006; Manikkam et al. 2008). While anthropologists have taken advantage of these approaches, they have also offered more grounded data, that is to say they offer data that link populations to contextual experiences in a host of settings with some new research that examines causal pathways.

The first approach to revealing early life calibration and sensitivity to context that I will highlight is innovation in research designs. One excellent example of this approach includes the assessment of reproductive hormonal profiles of migrant women who experienced different developmental environments than the one they were currently living in (Nunez de la Mora et al. 2007). By sampling across a spectrum of ages at migration, this research found that Bangladeshi women who migrated to England had lower salivary progesterone profiles and a later age at maturation when compared to second generation Bangladeshi migrants and women of European descent. Moreover, as might be predicted, the age at migration matters, with more time spent in Bangladesh having a stronger suppressive effect on adult progesterone profiles. As such, this research is one of the first to examine postuterine developmental experiences on reproductive hormonal profiles (Nunez de la Mora et al. 2007). Another noteworthy research design includes a post hoc test that links ponderal index (a proxy for fetal growth and fatness at birth) with heightened adult sensitivity to energetic constraint on estradiol (Jasienska et al. 2006b). This research was conducted among Polish women and examined the influence of activity levels on ovarian hormones by low, moderate, or high ponderal index at birth revealing a stronger suppressive effect with even moderate activity levels for women in the low ponderal index category. This research offers one of the first direct tests of early life programming and adaptation (Ellison and Jasienska 2007; Jasienska et al. 2006a).

The second approach to highlighting the invisible nature of biological embedding within anthropology includes advances in minimally invasive field techniques (see McDade 2014; Miller et al. 2013). While such field methods have been used for over two decades, new techniques allow for a wider array of biomarkers but also more direct evidence to apply to life history questions (McDade 2014; Miller et al. 2013). For example, given the emerging evidence for cues of local ecology and maternal condition in milk (Petherick 2010), studies examining hormonal cues and variation in the composition of breast milk are an exciting new area of research (Miller et al. 2013). Interesting developmental programming questions can be addressed directly from studies of milk (e.g., Hinde and Capitanio 2010; Hinde and Milligan 2011; Prentice 2005; Quinn and Kuzawa 2012). Milk analyses are

highlighted because they create the opportunity to test mechanisms of biological embedding while also linking women's daily lives to the biological experiences of their infants. For example, Quinn and Kuzawa (2012) found poor maternal nutrition was not reflected in macronutrient content of the breast milk of Filipino women but found docosahexaenoic acid (DHA) levels, important for neurological development, increased proportionately with increased fish consumption (Quinn and Kuzawa 2012).

Finally, while longitudinal cohort studies have long been the gold standard for understanding health across the life span, two merit mentioning for the ways in which the invisible nature of biological embedding can be revealed. The Cebu longitudinal study (Adair et al. 2011) offers the opportunity to ask intergenerational, early developmental, and longer term health questions. Considerable population level evidence for the effect of developmental processes on markers of stress, inflammation, and reproductive function are emerging from this important longitudinal study. For example, Kuzawa et al. (2010) found that rapid growth in the first 6 months of life meant greater investment in testosterone production and reaching puberty at an earlier age. Also McDade et al. (2010) found that low birthweight is linked to higher C-reactive protein, a marker of inflammation that is associated with a higher risk for cardiovascular disease Yet, overall, C-reactive protein may be lower in the Philippines than in the US due to pathogen exposure during infancy. Of particular note given the rare nature of longitudinal studies from sub-Saharan Africa is the Mandela's Children: the 1990 Birth to Twenty Cohort study (BT-20) (Richter et al. 2007). Similar to the Cebu study, the BT-20 study also documents communities experiencing a dramatic economic and nutritional transition. However, this cohort represents a very different daily lived experience. Born 4 years prior to the end of apartheid, the children in this cohort experienced considerable heterogeneity in nutrition, health, violence, and educational opportunities. Interesting insights have emerged from this study, including minimal differences in psychological well-being as a result of poor early life nutrition, a finding that stands in contrast to associations found in the US (Sabet et al. 2009). Also, similar to other findings, poor glucose tolerance is more common in children who were born with low birthweight and have higher body mass index levels at age 7 years (Crowther et al. 1998).

What Does this Embedding Approach Suggest for Work in Global Contexts?

In the search to reveal the processes that allow context to become biology, it is easy to lose sight of the fundamental implications behind the biological embedding approach. The distinctions between biology and environment can be artificial and misleading (Gravlee 2009; Oyama et al. 2001) because they suggest that biology can unfold in a vacuum (Oyama 2000), ignoring the very real physical and

emotional experiences associated with every environment from the most nurturing, to the poorest, or the most violent. Ultimately, we are examining women's (and men's) lived experiences and how these experiences shape the next generation's physical and emotional well-being. The ability to link biological embedding processes across time and space to intergenerational biological "memories" (Prentice 2001; Thayer and Kuzawa 2011) such as hunger and famine (Lussana et al. 2008; Tobi et al. 2009), to life span trade-offs such as shorter telomeres (markers of cellular aging) associated with chronic stress (Epel et al. 2004), and early life experiences of violence (Shalev et al. 2013) creates the opportunity for more robust public health interventions.

As researchers committed to context, perhaps our biggest challenge is to document the invisible nature of constraints to care and nurturing (Pike 2014) that women and men in marginalized communities experience. Or perhaps most poignantly, as Rudzik's work among poorer women in Sao Paulo, Brazil, suggests even the circumstances of whether or not a woman wanted or planned the pregnancy influences levels of oxytocin and stress hormones, which in turn can influence glucocorticoid levels in breast milk (Rudzik 2013; Rudzik et al. 2014). Or, as is emerging in the obesity literature, constraints to nurturing may also include how to make (and afford) healthy food choices in a constantly changing food and nutritional environment. Such challenges to feeding children have emerged across the globe (Adair and Popkin 2005). Indeed the work of Thompson et al. (2014), Thompson (2013), and Wasser et al. (2013) suggest important challenges for US families too, with patterns of childcare linked to infant feeding and obesity. These examples offer an important snapshot of the invisible processes that women and children, in particular, experience regularly, but they also offer the first steps in how to link the biological embedding of context with daily lives in more nuanced ways.

How then can we leverage these findings of the importance of biological embedding of context to the global sites of inequality that many of us work in? The sites I work in, as an example, represent one extreme end of a nutritional continuum, with low nutrition driving thriftier developmental pathways. In this very real backdrop of marginalization and inequality, might there be testable questions that make it clear that the starting point for intervention involves monitoring growth and development across early life and into middle childhood and adolescence? Laudable steps are being taken to examine the impact of psychosocial well-being on pregnancy outcomes (e.g., Dancause et al. 2011; Howells 2013; Thayer and Kuzawa 2014) and how local dietary shifts influence breast milk composition (Quinn and Kuzawa 2012). It is reasonable, then, to expect the emergence of new developmental questions that directly address the circumstances associated with contexts of global inequality. As scholars trained to scrutinize the links between context and biology, we have the opportunity to be at the forefront of generating these new questions.

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