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Preterm Birth

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Synonyms

Gestation; Premature birth; Prematurity; Preterm labor

Definition

Preterm birth is defined as babies born alive before the completion of 37 weeks of pregnancy.

Introduction

Preterm birth (PTB) is the leading cause of death in children under five worldwide and its complications are responsible for the deaths of approximately one million children annually. Babies born too soon are predisposed to suffer from neurodevelopmental, respiratory, gastrointestinal, and other complications throughout their lives. Both heritable and environmental risk factors contribute to PTB, and although PTB can be associated with medical disorders such as preeclampsia or intrauterine growth restriction, most cases of PTB occur spontaneously and lack an obvious cause. Ultimately, why spontaneous PTB occurs in humans remains largely a mystery, but important clues can be found in the evolution of the traits and trade-offs that have shaped human pregnancy.

The Burden of Preterm Birth

PTB is a complex, multifactorial syndrome associated with multiple mechanisms of disease and many causes (Goldenberg et al. 2008; Muglia and Katz 2010; Romero et al. 2014; Vogel et al. 2018). Generally defined as birth before 37 weeks of gestation or 259 days since a woman's last menstrual period (Vogel et al. 2018), PTB can be caused by: (1) the medically indicated induction of preterm delivery due to either maternal or fetal complications, (2) preterm premature rupture of membranes (PPROM), or (3) spontaneous, idiopathic preterm labor with intact fetal membranes (sPTB). Approximately, a third of all preterm births are medically indicated due to preeclampsia (PE), intrauterine growth restriction (IUGR), gestational diabetes mellitus (GDM), chorioamnionitis, or other complications. Of primary concern for reducing rates of prematurity is understanding the causes of the remaining two thirds of preterm births occur in the absence of any obvious risk factors (Goldenberg et al. 2008; Vogel et al. 2018). PTB is a global problem with rates that range as high as ~18% in low-income countries to

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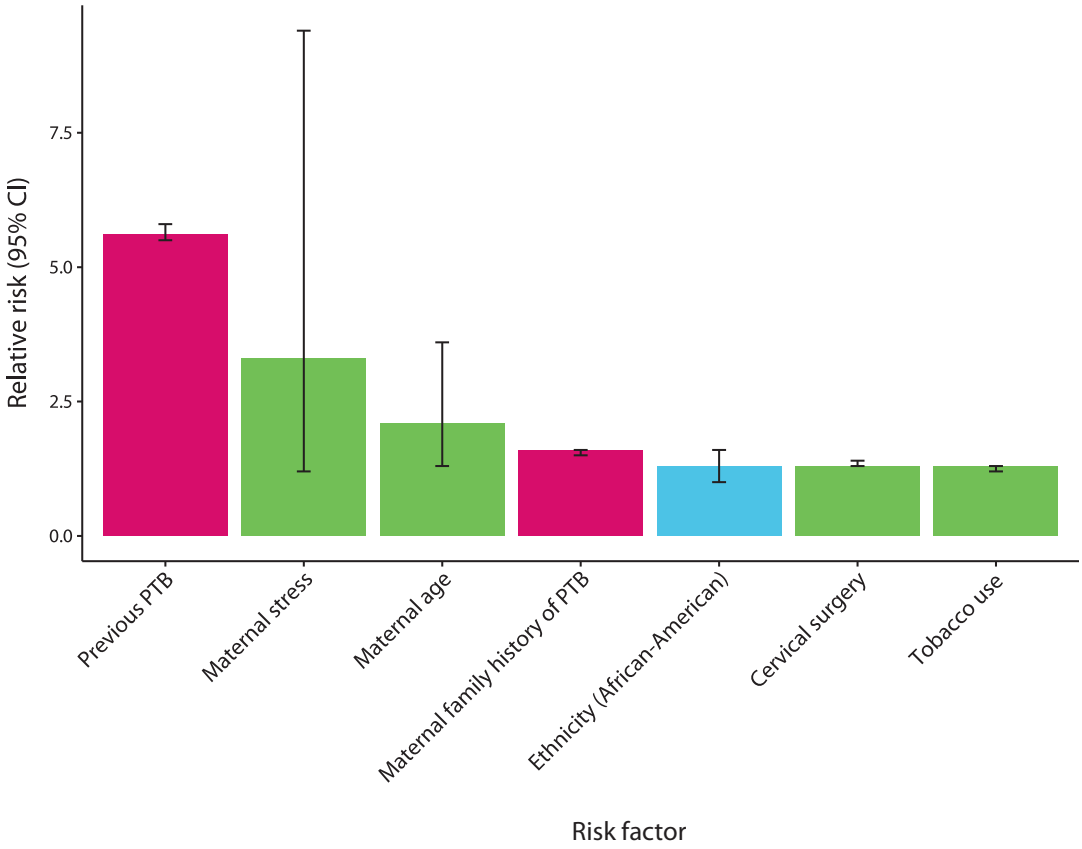
lower rates in high-income countries (~5%) (Blencowe et al. 2013), and a global prevalence around 10% (Vogel et al. 2018).

Efforts to reduce the rates of PTB have only met with mixed success. In the United States, for example, the rate of preterm birth has increased by 30% since 1981, reaching its peak at 12.5% in 2006, with the rate currently reported at 9.6% (Blencowe et al. 2013). Recent estimates indicate that complications of PTB are the leading causes of death of children below 5 years of age globally (Vogel et al. 2018). In what follows, we summarize some of the risk factors associated with PTB, and then address more ultimate questions about why variation in birth timing might occur in the first place, which requires that we take an evolutionary perspective on birth timing. There are many reviews that discuss what is known about preterm birth from more molecular, clinical, and obstetrical perspectives, such as Goldenberg et al. (2008), Romero et al. (2014), Swaggart et al. (2015), Di Renzo et al. (2018), Strauss et al. (2018), and Vogel et al. (2018).

In one comprehensive review, Romero et al. (2014) summarized the growing consensus that PTB does not represent a single disease, but a syndrome with many causes. The causes of the PTB syndrome are complex with multiple genetic and environmental risk factors at play (Fig. 1). Epidemiological studies have linked poverty, education, age, body mass index, marital status, prenatal care, rates of multiple births, tobacco use, and other factors with PTB incidence (Goldenberg et al. 2008). A particularly important risk factor for PTB is intrauterine infection: about one out of every four pre-term births is associated with infection (Romero et al. 2001). Intrauterine infections can cause PTB by activating the innate immune system and triggering the release of inflammatory proteins, such as cytokines and chemokines, that can lead to premature labor (Goldenberg et al. 2008). Maternal medical conditions that have been shown to increase PTB risk include thyroid disease, asthma, hypertension, diabetes, periodontitis, a history of prior preterm birth or cervical loop procedures, and depression (Goldenberg et al. 2008; Cobb et al. 2017). Finally, PTB risk has also been shown to be associated with maternal age, and women under 20 and over 40 are more likely to deliver preterm (Boardman 2008).

There is clearly a role for genetics and epigenetics in PTB risk (York et al. 2014; Monangi et al. 2015; Strauss et al. 2018). Twin studies have demonstrated both maternal and fetal genetic contributions to PTB risk, with heritability estimated between 15% and 40% (Clausson et al. 2000; Treloar et al. 2000; Kistka et al. 2008). More recently, York et al. (2014) summarized the contribution of fetal (11–35%) and maternal (13–20%) genetic factors based on European and European-American datasets. A woman's risk of delivering preterm is increased if her mother, full sisters, or maternal half-sisters have delivered preterm (Boyd et al. 2009). PTB risk also differs between ethnic groups. For example, the PTB rate among black women in the United States is twice as high as the rate among white women, even after adjusting for other confounding factors (Adams et al. 1993; Collins et al. 2007; Kistka et al. 2007). Conversely, East Asian and Hispanic women have relatively low rates of PTB, whereas South Asian women have increased risk of low birth weight with no connection to PTB risk (Goldenberg et al. 2008). The factors contributing to the observed racial disparities in PTB rates remain unresolved, and although some of the racial disparities in PTB rates are likely to be genetic, both novel environmental risks and epigenetic factors may play important roles (York et al. 2014; Barcelona de Mendoza et al. 2017).

Not much is yet known about identifying the genetic variants that contribute to PTB risk, because most of the variants that have been discovered have either yielded conflicting results or have failed to be replicated (Strauss et al. 2018; Vogel et al. 2018). In a recent exciting development, Zhang et al. (2017) performed a genome-wide association study that led to the reliable identification of variants in six loci (*EBF1*, *EEFSEC*, *AGTR2*, *WNT4*, *ADCY5*, and *RAP2C*) that were significantly associated with gestation length and of variants in three loci (*EBF1*, *EEFSEC*, and *AGTR2*) that were significantly associated with PTB, opening the door for



Preterm Birth, Fig. 1 PTB risk factors. Risk factors for PTB stem from genetics (pink), environmental stress (green), and ethnicity (blue). Redrawn from Bezold et al. (2013) where relative risk and confidence intervals were obtained from previous independent PTB risk studies applying a variety of methods

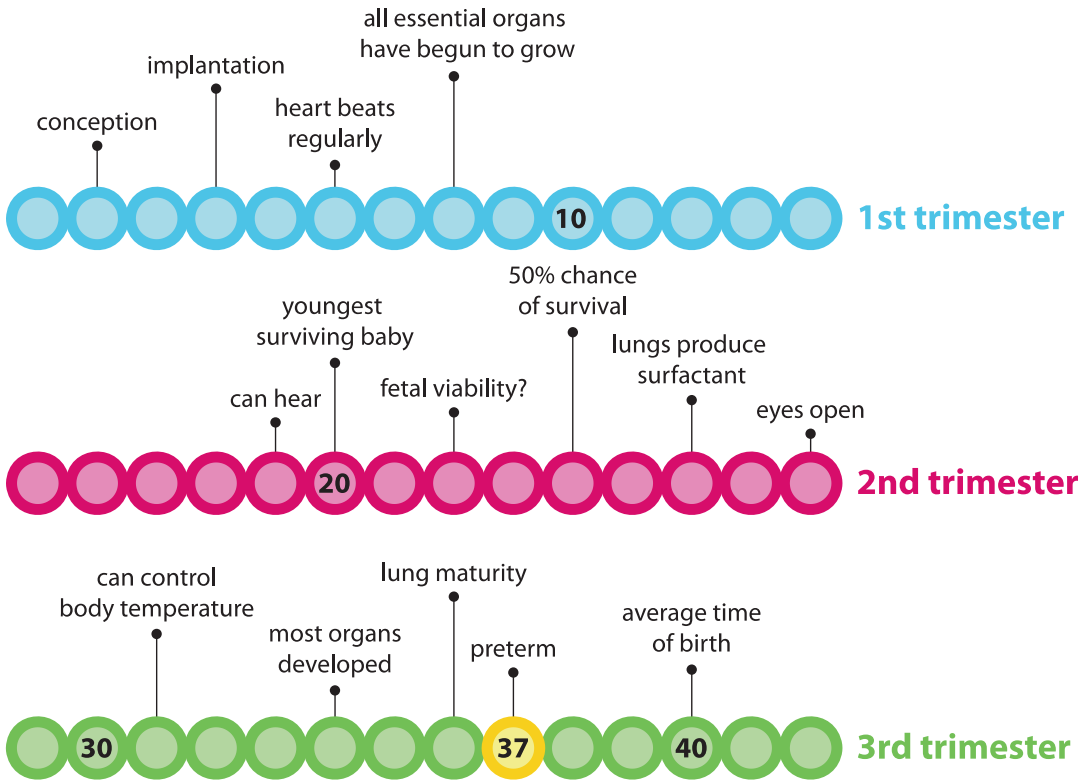
functional studies that shed light into the molecular mechanisms underlying PTB.

Long-term cohort studies have been particularly important in understanding the consequences of low birth weight and preterm birth for adolescents and adults. An important longitudinal dataset known as the Helsinki Birth Cohort Study (HBCS) has provided many insights. The HBCS comprised 13,345 subjects from 1933 to 1944 with associated metrics that span prenatal to adult life. Another study that is beginning to yield results is the Born in Guangzhou Cohort Study, which has been tracking 33,000 Chinese babies and mothers since 2012. Data derived from the HBCS have provided important insights into the origins of disease in early life, including how low birth weight and premature birth increase risks of a variety of adolescent and adult diseases (Thornburg and Marshall 2015; Cyranoski 2018). Finally, some risk factors for PTB overlap with other inflammatory diseases such as inflammatory bowel disease or periodontitis, indicating strong gene x environment interactions that perturb general physiological and immunological processes involved in women's health (Strauss et al. 2018).

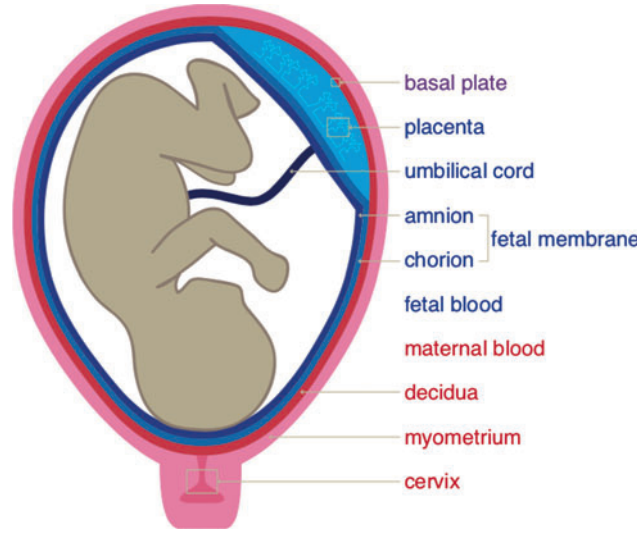
Clearly, many risk factors have been identified for PTB, but PTB remains disturbingly common. The majority of preterm births occur without any obvious risk factor and most risk factors are only weakly associated with PTB. Despite decades of effort, rates of PTB remain remarkably high or on the increase in many regions in the world, with variable patterns and etiologies that defy easy explanation (Byrnes et al. 2015; Vogel et al. 2018). One of the fundamental challenges in

mitigating the risk of PTB is that the distinction between normal labor and prematurity is likely extremely subtle, and common pathways are at work in each (Romero et al. 2006). (Fig. 2). In the case of normal term labor, parturition is the result of complex uterine and extra-uterine factors (e.g., hormones) that physiologically activate "parturition complex cascade" (Di Renzo et al. 2018). In the case of premature labor, these same factors are disrupted, and as Romero et al. (2006) put it, are activated in a manner that can be described as "extemporaneous."

This implies that understanding human gestation timing and PTB is tantamount to understanding not only human pregnancy but because pregnancy research involves animal models, mammalian pregnancy more generally (Carter 2007; Phillips et al. 2015; Swaggart et al. 2015; Eidem et al. 2017). This is an enormous task, and the challenge of resolving PTB is entangled in the remarkable complexity of pregnancy itself. For example, pregnancy is the only physiological process where the cells of two genetically distinct individuals of the same species come into such prolonged and intimate proximity. In order to succeed, it requires elaborate physiological cooperation and coordination between mother and child, under conditions that range from the adverse to benign. Unexpectedly however, pregnancy is riddled with indications of difficulties and conflict. Less than 50% of conceptions result in pregnancy in humans, a rate higher than other mammals (Macklon and Brosens 2014). More dramatically, pregnancy remains one of the leading causes of female mortality worldwide. In 2013, the United Nations and World Health Organization estimated that a woman died about every 2 min from causes related to pregnancy or childbirth (Say et al. 2014). Although there are diverse causes, chief among them are excessive bleeding after childbirth, high blood pressure during pregnancy (pre-eclampsia and eclampsia), and



Preterm Birth, Fig. 2 Human pregnancy timeline. Normal human pregnancy lasts approximately 40 weeks. Delivery is considered preterm before 37 completed weeks of gestation



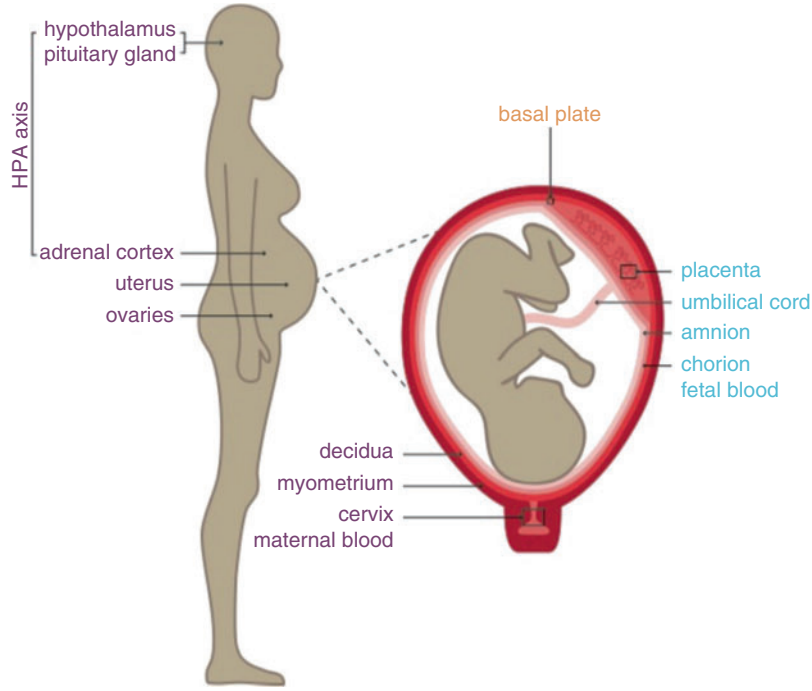
Preterm Birth, Fig. 3 The tissues of pregnancy. Note that some tissues are of maternal origin (cervix, myometrium, decidua, and maternal blood; shown in red), others are of fetal origin (fetal blood, fetal membranes, umbilical cord, and placenta; shown in blue), and one is of mixed maternal and fetal origin (basal plate; shown in purple)

difficult childbirth (Say et al. 2014), much of this can be pinned on (1) the deeply invasive nature of placentation in humans, and (2) the unusually large size of encephalized fetus at birth. As described in more depth below, both have important implications for understanding birth timing in humans (Rosenberg and Trevathan 2002; Dunsworth and Eccleston 2015). The common pathways that underlie pregnancy and PTB, and the unique features of human pregnancy, mean that understanding PTB requires a broad consideration of the evolution of pregnancy itself.

Human Pregnancy, in Brief

Humans are viviparous mammals – they have live birth. Live birth is not unique to humans or to mammals, however (Abbot and Rokas 2017). Viviparity has evolved over 150 times independently in vertebrates alone and occurs in invertebrates as well (Blackburn 2014; Wagner et al. 2014). Viviparity requires the development of means to nourish developing embryos and channel waste products away within the mother's body, and all eutherian mammals express *placental matrotrophy* – embryonic provisioning by maternal secretions by way of a transient, vascularized organ that attaches to the endometrial lining of the maternal uterus known as the placenta (Trexler and DeAngelis 2003; Fig. 3). In eutherian mammals, the placenta accomplishes many of the fetal functions performed by the major organs in newborns, including exchange of oxygen and carbon dioxide, the secretion of endocrine, growth factors, and cytokines, and the transport of nutrients and elimination of wastes (Burton and Fowden 2015; Nelson 2015). The eutherian placenta also has important endocrine functions as well, modulating maternal metabolism and the immunological response to pregnancy, while maintaining uterine quiescence (De Bonis et al. 2012). The centrality of the placenta is highlighted by the fact that, in the very first days following fertilization, the majority of embryonic cells in the growing blastocyst are placental (Norwitz et al. 2001). The *chorioallantoic* placenta of eutherians is so-called because, soon after the blastocyst implants into the uterine wall, the fetal membrane that forms the embryonic bladder and stores fetal excretions, or allantois, fuses with and vascularizes the chorion, the outermost membrane involved in gas exchange that surrounds the embryo (Fig. 4).

Following conception, implantation of the blastocyst in the uterine endometrium involves penetration by the embryonic trophectoderm (the precursor to the placenta) onto the uterine endothelial cells (Schlafke and Enders 1975). In most mammals, blastocyst implantation is shallow and



Preterm Birth, Fig. 4 Pregnancy uniquely requires communication and coordination across multiple tissues in two individuals. Multiple maternal tissues (written in purple font) and fetal tissues (blue) as well as tissues comprised of both maternal and fetal cells (orange) must interact to facilitate a healthy pregnancy. The placenta serves as the nexus of communication that links multiple tissues in the mother and fetus both locally and at a distance. For example, interactions between NK cells in the decidua and fetal trophoblast cells in the placenta shape the degree of placental invasiveness and rate of the exchange of nutrients and oxygen. Similarly, the hypothalamic–pituitary–adrenocortical (HPA) axis communicates maternal and fetal stress levels across multiple tissues through cortisol shared through blood exchange in the placenta

superficial, and six tissue layers separate maternal and fetal blood (Gundling and Wildman 2015). In some however, including humans, the blastocyst embeds deeply and is engulfed interstitially by the maternal endometrium. Placental traits widely vary between mammalian groups (Martin 2008). In the *hemochorial* placenta of primates, rodents, and bats, the placental trophoblast cells invade the uterine lining, eroding and remodeling vascular tissues, facilitating the bathing of placental villi in maternal blood (Gundling and Wildman 2015; Burton et al. 2016). In humans, placentation is particularly invasive, and the remodeling of maternal blood vessels is exaggerated (Burton et al. 2016). When maternal arterial remodeling is poor, reduced uteroplacental arterial flow to the placenta is followed by a cascade of potential consequences in response to fetal signals of distress, including inflammation, hypertension, kidney damage, and proteinuria in the mother, and an increase in oxidative stress and spontaneous PTB in the fetus, with a poor prognosis for both mother and fetus if untreated, and potentially life-long consequences for survivors (Redman and Sargent 2005; Thornburg and Marshall 2015). On the other end of the spectrum, the leading cause of maternal mortality is postpartum hemorrhaging (PPH), which results from improper separation of the placenta form the uterine wall, leading to massive maternal blood loss (Abrams and Rutherford 2011). PPH rarely occurs in mammals, and the degree with which it occurs appears unique to humans (Abrams and Rutherford 2011). Abrams and Rutherford (2011) summarize evidence that suggests that PPH results from an overly aggressive placental

invasion and vascular remodeling of maternal tissues, increasing the chances of impaired separation. Preeclampsia and PPH are but two of many disorders of pregnancy resulting from improper placentation, and as discussed further below, evolutionary perspectives provide unique insights into the factors that have led to the delicate maternal/fetal balance, and the complexities of birth timing (Abrams and Rutherford 2011; Thornburg and Marshall 2015).

Parturition involves a transition in the maternal myometrium from a state of anti-inflammatory quiescence to a pro-inflammatory contractile state. How this is accomplished varies across mammals, but generally involves dynamic interactions between pro-inflammatory prostaglandins and the inflammation-suppressive effects of the steroid hormone progesterone (P4) (Swaggart et al. 2015). In humans, apes, and monkeys, P4 production is high throughout pregnancy and acts to repress pro-inflammatory genes. Towards the onset of parturition, increased expression of microRNAs (miR-200 family) induce functional progesterone withdrawal, the de-repression of inflammatory chemokine and cytokine pathways, and the production of contraction-associated proteins such as oxytocin and prostaglandin receptor (Di Renzo et al. 2018). Cervical ripening and changes in maternal inflammatory/proteolytic factors in decidual and uterine membrane mark the withdrawal of decidual support for pregnancy, culminating in membrane rupture and the onset of vaginal birth (Di Renzo et al. 2018). Preterm birth involves congenital or acquired agents that distort or disrupt this common template.

With respect to the evolution of pregnancy, there are two key trends. First, pregnancy-related genes and phenotypes have changed dramatically fast over evolutionary time and have often evolved independently, giving rise to convergence (Wildman et al. 2006; Wildman 2011; Wagner et al. 2014). The high evolutionary rate and convergence make studying the evolution of human pregnancy particularly challenging, because similarity in pregnancy phenotypes among distant relatives cannot be assumed to reflect the ancestral phenotype. For example, hyraxes, like humans, have highly invasive placentas, whereas elephants and lemurs have noninvasive ones, even though humans and lemurs are closer relatives to each other than to hyraxes and elephants (Wildman et al. 2006). Equally, there is variation in endocrine patterns as well. Levels of the hormone progesterone rise throughout gestation in humans and the great apes, but not in closely related Old World monkeys, nor in other mammals generally (Carter 2007; Grigsby 2016). What these patterns indicate is that even close evolutionary affinity cannot be used to infer similarity in phenotype (Swaggart et al. 2015).

Evolutionary Perspectives on Birth Timing in Humans

The persistence of complex heritable diseases like PTB that causes reproductive deficiencies or even untimely death is paradoxical, because these diseases seem to favor their own demise (Brown et al., 2013). Why is there heritable variation in birth timing in humans? Evolutionary perspectives on medicine are predicated on the idea that human diseases emerge out of the evolutionary challenges inherent to fitting complex biological systems to diverse and shifting optima (Gluckman and Hanson 2006; Nesse et al. 2012; Stearns and Medzhitov 2015). Nesse et al. (2012) outline six broad and interrelated categories of evolutionary explanations for traits that predispose humans to noncommunicable diseases. We highlight three of these for PTB. The first is **mismatch** between our biological legacy and our modern environments, as in the case of diaper rash (Gluckman and Hanson 2006; Corbett et al. 2018). Mismatch between our biological designs for ancestral environments and modern lifestyles accounts for many common diseases such as obesity, addiction, diabetes, or heart disease. Disruption of normal pregnancy may reflect a mismatch between our modern lifestyles and our biological designs. A second explanation, related to evolutionary constraints, is that of **trade-offs**, the idea that there are combinations of traits that cannot be simultaneously optimized by natural selection (Rickleffs and Wikelski 2002; Stearns and Medzhitov 2015). For example, many fitness-related traits draw on common energetic reserves, and investment in one comes at the expense of the

other (Zera and Harshman 2001). An example is large body size, which may improve survival, but comes at the expense of numerical investment in reproduction. Finally, a third explanation is that of **evolutionary conflicts**. All multicellular organisms are aggregates of genes, cells, tissues, and organs; natural selection can act differently on any individual member or level, giving rise to evolutionary conflicts (e.g., a mutation that may favor cell division and propagation of the gene that carries it may not be advantageous for the tissue or organ, as in cancer) (Queller and Strassmann 2018). Conflicts over pregnancy may be particularly acute in humans, because of the invasive nature of placentation and that natural selection can act differently in parents versus offspring. Below, we consider each of these explanations in more depth.

Mismatch and PTB

Some environmental influences on birth timing, such as tobacco use, represent modern causes of PTB that can be thought of as mismatches between the conditions our pregnant bodies were designed for, and the ones that our modern lives too often provide (Crump et al. 2011; Corbett et al. 2018). Many environmental risk factors probably fall in the category of causes that almost certainly emerged within modern times, and to which humans are poorly adapted. For mismatches that affect the outcome of normal pregnancy, there should be selection for traits that protect against maternal or fetal harm. Indeed, there is evidence not only that humans have experienced on-going natural selection on pregnancy-related traits but evidence of population-specific variation as well (Brown et al. 2013). An illustrative example can be found in preeclampsia (Ben et al. 2016). Modern changes in diet and nutrition may be a source of "mismatch" between contemporary diets and maternal physiological adaptations for pregnancy. Risk for preeclampsia varies inversely with salt intake, and paradoxically, rates of preeclampsia are low in countries such as Japan and Iran, where salt-intake is high (Brown et al. 2013). Brown et al. (2013) suggest that women in high salt-intake countries may have experienced selection for insensitivity to high-salt diets, conferring some protection against preeclampsia. In the absence of such insensitivity, the high-salt diets characteristic of Western societies represent evolutionary mismatches with potentially severe consequences for affected pregnant women. Like preeclampsia, PTB also exhibits population-specific, ethnic and racial variation similar to preeclampsia, raising the hypothesis that mismatches contribute to its high incidence.

One intriguing pattern is that it is not clear whether several of the known, important environmental risk factors for PTB, such as maternal nutrition and stress, represent entirely modern perturbations of pregnancy. In a meta-analysis of 78 studies on maternal body mass index (BMI), Han et al. (2010) showed that low maternal BMI was associated with increased risk of both PTB and low birth weight. Likewise, in a systematic review of 39 studies, Staneva et al. (2015) concluded that psychosocial factors, such as maternal stress during pregnancy, can have a profound effect on birth outcomes. Glucocorticoids increase towards the end of pregnancy and are important for maturation of fetal organs. However, maternal stress can elevate glucocorticoids, which cross the placenta and result in reduced fetal growth rates (Thornburg and Marshall 2015). There is also evidence of racial differences in stress-induced inflammatory responses that are linked to PTB risk (Christian et al. 2013). In animal models, both nutrition and stress have adverse effects on birth outcomes. In rodents for example, various forms of stressors, from hypoxia to social stress via dominance interactions with conspecifics, can result in reduced litter sizes, smaller birth weights, selective reabsorption/abortion of fetuses, and various alterations of fetal developmental programs with adverse postnatal effects in offspring (Brunton 2013). While the mechanisms underlying these effects are not fully understood, conserved elements of the vertebrate neuroendocrine systems that regulate response to stress (e.g., the hypothalamo-pituitary-adrenal or HPA axis) are centrally involved.

That adverse pregnancy outcomes could display such sensitivity to environmental variation, mediated by broadly conserved vertebrate stress responses, has led to various evolutionary

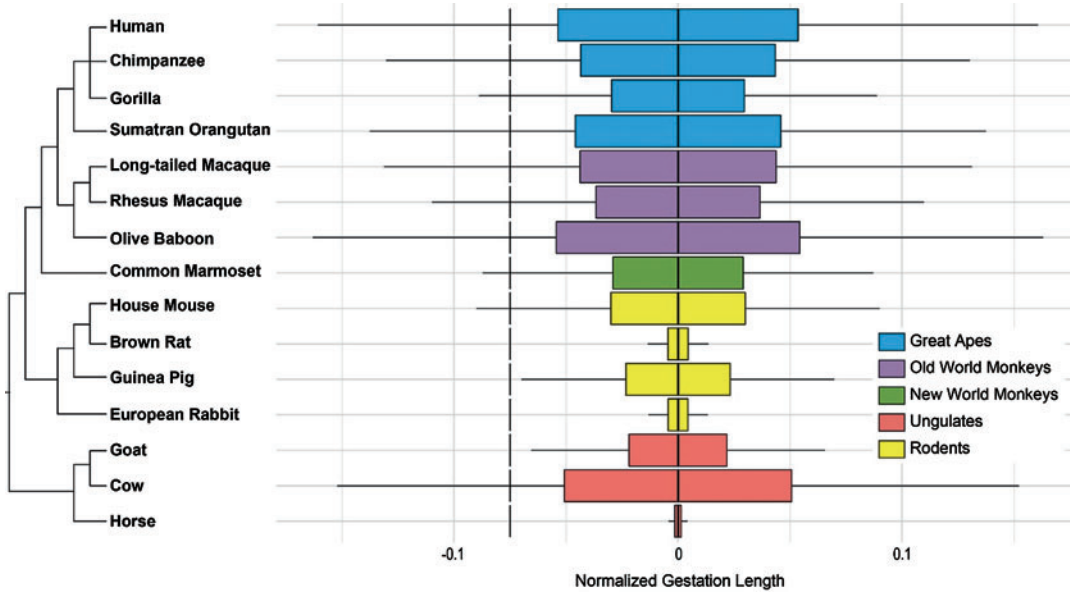
hypotheses that propose adaptive maternal/fetal mechanisms for inducible plasticity in birth timing (Gluckman and Hansen 2006). Plants and animals can alter phenotypic traits in response to environmental cues, a phenomenon known as *phenotypic plasticity*, and this can happen not only in adults but over the course of development as well (Via and Lande 1985). Crespi and Denver (2004) draw on abundant evidence for phenotypic plasticity in animals, encoded by conserved genetic and physiological mechanisms that predate modern human origins, to propose that at least some of the variation in birth timing in humans might reflect similar plastic responses to environmental input. Indeed, variation in birth timing is the rule, not the exception, in animals (Phillips et al. 2015) (Fig. 5). The mammalian HPA axis matures during the third trimester in humans, with a rise in stress hormones that regulate fetal development and prepare the maternal and fetal membranes for parturition (Crespi and Denver 2004). The months leading up to parturition are characterized increasingly by a finely-tuned period of stress sensitivity. In this view, both maternal and fetal fine-tuning of the rate of fetal development and/or parturition in response to such factors as nutrition or stress might reflect a form of adaptive plasticity in birth timing. To the extent that pregnancy is costly and that its costs vary with external conditions, maternal and fetal mechanisms may be present for navigating the course of pregnancy in a way that minimizes those costs, especially in conditions in which pregnancy outcomes are uncertain (McLean et al. 1995; Wells 2003; Pike 2004). Haig (2008) has suggested that mother and fetus may differ in plastic adjustments to gestation length, depending on environmental conditions. Romero et al. (2014) make a similar point, that PTB in response to intra-amniotic infection likely has some survival value for both fetus and mother. Thus, it seems reasonable to hypothesize that some adverse birth outcomes, including some cases of PTB, may be due to mismatch between conditions that alter the maternal microbiome and birth outcomes (Chu et al. 2018). The major etiological roles of vaginal, intrauterine, and periodontal infections in PTB, and the organizing role of maternal inflammatory/immunological responses in pregnancy and labor, strongly implicate a microbial x environment interaction in pathologies of pregnancy. Indeed, four of the loci identified by Zhang et al. (2017) with variants conferring risk for gestation length or PTB, two (*EBF1* and *EEFSEC*) likely are involved in inflammatory pathways, albeit indirectly (Romero et al. 2006; Strauss et al. 2018).

In summary, an evolutionary restatement of the "common pathway" hypothesis for PTB could be as follows: PTB is the result of a mismatch between ancient, conserved biological mechanisms for orchestrating of birth timing in viviparous mammals in response to once-reliable cues that are now absent or miscalibrated by modern lifestyles.

Trade-Offs and PTB

Evolutionary anthropologists have long hypothesized that two human traits interact to determine birth timing (Trevathan 2015). One is our big brain size, which has resulted in remarkably encephalized infants at birth relative to other primates. The other is our bipedalism, which has resulted in the remodeling of our pelvic girdles to accommodate our upright stance. Trade-offs and constraints lie at the root of a branch of evolutionary biology known as *life history theory* (Zera and Harshman 2001; Rickleffs and Wikelski 2002; Roff and Fairbairn 2007). Life history traits are those that characterize the patterns of organism survival and reproduction, such as age at first reproduction and body size. A tenet of life history theory is that these traits are interrelated and often negatively correlated. Large body size may increase offspring survival probabilities, for example, but it comes at the expense of risking dying before reproducing, since large bodies take longer to build. Natural selection is assumed to act on life history traits collectively, as if they each were constrained by the competing demands of the others, and the solution is a compromise.

With respect to birth timing in humans, one leading hypothesis, known as the *Obstetric Dilemma* (OD), is that gestation length is governed by a trade-off between brain size and pelvic proportions, and occurs at the point at



Preterm Birth, Fig. 5 Within species variation in gestation length among representative primates and mammals. Boxes denote the range of values encompassed by 1 standard deviation from the mean in either direction; whiskers extend to 3 standard deviations. The dotted line corresponds to 92.5% completed gestation time. (References for each species' data can be found in Phillips et al. (2015))

which the head of a big brained fetus can barely fit through the narrow pelvic girdle of a bipedal-adapted female (Wells et al. 2012). This is proposed to account for the observation that, among primates, human neonates are particularly developmentally immature, with brain to body ratios the smallest among all primates (Rosenberg and Trevathan 2002). More recently, a competing hypothesis, known as *Energetics of Gestation and Growth* (EGG), argued that birth timing is set by the point at which it becomes metabolically inefficient for the mother to nurture the fetus within her uterus relative to the provision she could accomplish after birth (Dunsworth et al. 2012). Both hypotheses invoke constraints and trade-offs in the ability of mothers to optimize neonate development in utero. The key point is that for any trait governed by trade-offs, outcomes can be precariously balanced between opposing demands, and changes to one demand can result in pathological over- or under-compensation in the others (Crespi 2010; Crespi and Go 2015; Quellller and Strassmann 2018). If PTB is governed by trade-offs, the implication is phenotypic variation in birth-timing may be maintained because of how biotic and spatio-temporal variation affects the functional compromises required during pregnancy.

A particularly important trade-off in animals is between immunity and other energetically expensive traits, such as growth or reproduction. Maintaining or mounting immune and inflammatory responses comes at a cost to other physiologically demanding needs. Immunity trade-offs can have profound effects. For example, Urlacher et al. (2018) showed that in a population of Amazonian forager-horticulturalists, children who experience only mildly elevated immune responses can have as much as a 49% reduction in growth rate, resulting long-term differences in stature and likely other developmentally dependent traits. Such direct effects of immunity and inflammatory responses on human phenotypes may have particular relevance to pregnancy and birth timing.

As described above, mammalian reproduction has been superimposed on ancestral immune factors, which have been co-opted for key roles in the

relatively more recent development of internal fertilization, placentation, and gestation (Abrams and Miller 2011; Bainbridge 2014). Early views on the role of immunity in pregnancy centered on the idea that the maternal immune responses must be suppressed in order to tolerate pregnancy, an observation that formed the rationale for Medawar's famous *allograft model* for mammalian pregnancy in which antigenically foreign fetal membranes are like grafts onto maternal tissues, requiring mechanisms for tolerance (Medawar 1953). While Medawar's model captured elements of the immunological challenges posed by the particularly long gestation involved in human pregnancy (Bainbridge 2000), the modern view of the role of the maternal immune system in mammalian pregnancy is dramatically different. Inflammatory and immunological pathways are central to understanding the mechanisms that determine birth timing and parturition in humans (Moffett and Loke 2004; Trowsdale and Betz 2006; Abrams and Miller 2011; Mor et al. 2011; Romero et al. 2014). Maternal immunity first and foremost must protect against infections and pathogens. However, human reproduction involves cycles of up and down-regulation of immunological and inflammatory factors governed by reproductive hormones (Abrams and Miller 2011; Alvergne and Tabor 2018). Over the course of pregnancy, dynamic shifts in immunity are required for successful pregnancy (Abrams and Miller 2011). Fetal tolerance is promoted by the absence of MHC alloantigens on the fetal trophoblast cells. At the same time, the early stages of pregnancy bear many of the hallmarks of tissue injury, including a sustained maternal inflammatory response that underlies the all-too-familiar morning sickness (Macklon and Brosens 2014; Griffith et al. 2017; Ashary et al. 2018). Pro-inflammatory cytokines that induce cell-mediated immunity are down-regulated during pregnancy, leaving pregnant women more vulnerable to infectious diseases (Abrams and Miller 2011). Placental inflammatory responses vary with maternal body mass (Thornburg and Marshall 2015). With the onset of labor, increased catabolism of progesterone, which suppresses the inflammatory response, is associated with a dramatic increase in inflammation, including the invasion of leukocytes into the myometrium, cervix, and feto-placental membranes (Abrams and Miller 2011). These shifts in maternal immunity over the course of pregnancy underlie the critical role that trade-offs between the dual and sometimes competing roles that immunity plays in female health and reproduction (Romero et al. 2001). Little surprise then that inflammatory pathways, and genetic variants that disrupt the carefully choreographed involvement of inflammation in normal labor and birth, are emerging as prime candidates for understanding the causes of spontaneous pre-term birth (Strauss et al. 2018).

Evolutionary Conflicts and PTB

Pregnancy should seem to be an entirely communal enterprise between mother and fetus. However, because of viviparity, placental traits reflect an evolutionary tug-of-war between parents and offspring over resources (Haig 1993). Matrotrophic nourishment in viviparous species implies that a developing fetus can negotiate with its mother over nutritive provisioning, something not possible in egg-laying species. An inevitable conflict arises in such cases, because in sexually reproducing species, the fetus only shares half of its genes with its mother, and in mammals that are not monogamous, less than half its genes with any future offspring that its mother may have. Mothers, on the other hand, are equally related to all of their offspring. Thus, the investment optima for mother and offspring can differ, with mothers maximizing total reproductive effort and each offspring favoring greater personal investment. The *viviparity conflict hypothesis* holds that many features of viviparity bear that signatures of parent-offspring conflict (Crespi and Semeniuk 2004). Indeed, as Crespi and Semeniuk (2004) point out, when the costs and benefits of matrotrophic viviparity are considered objectively, for offspring the benefits of starting out life nourished and sheltered within the uterus seem obvious, such as greater size and vigor at birth or avoidance of predation common to egg-laying species, and the costs few. But for mothers, the reverse is true. The direct apposition of maternal and fetal tissues over development thus seems

designed for the benefit of offspring, by providing the most efficient means of resource transfer.

Conflicts of pregnancy are most easily recognized in live-bearing animals, where dramatic examples such as intrauterine cannibalism found in various amphibians, sharks, and fish or selective abortion of excess, small, or impaired embryos can be found in many animals, including primates (Forbes 1997; Crespi and Semeniuk 2004; Catalano et al. 2018). In the case of selective abortion, the data are so abundant due to decades of selective breeding and work with laboratory models that it is known as *The Bruce Effect*, named after the researcher who first described adaptive reproductive suppression and selective abortion in pregnant females under conditions that signal declining prospects for gestating young (Catalano et al. 2017). Although controversial, the existence of a Bruce Effect in humans (spontaneous abortion of *periviable* infants before the 28th week of gestation) is supported by non-random patterns in spontaneous abortions, such as selection against morphologically, genetically, and chromosomally abnormal fetuses (Catalano et al. 2018). The larger implication is that gestation timing is not the result of a fixed program, but rather dynamic and highly sensitive to crosstalk between mother and infant informed by numerous inputs, including fetal health. As Catalano et al. (2018) put it, parturition in humans may be "strategic."

Conflict theories of pregnancy thus hold that mothers and infants can have opposing strategies. Recognizing this sheds light on many puzzling features of pregnancy, each with implications for understanding gestation timing and PTB (Haig 1993, 2008; Crespi and Semeniuk 2004). Some of these include: (1) the placental production of fetal hormones and other factors that manipulate maternal physiology and nutrient transfer, in many cases seeming to wastefully duplicate those produced maternally (Haig 1993); (2) evidence of maternal inactivation of placentally secreted factors (Haig 1993); (3) a shift in the production of pregnancy-promoting progesterone at 5–7 weeks of pregnancy from maternal ovary to the placenta, which is uncommon in other mammals (Pavličev and Norwitz 2017); (4) evidence of maternal mechanisms to regulate placental invasiveness (Heap 1994; Moffett and Loke 2004); (5) the rapid evolution and multiple independent origins of placental traits, including multiple origins and evolutionary convergence of invasive placentae, implying strong and ubiquitous selection, fast and positive selection on placental or maternal genes and genome features involved in pregnancy, and the evolutionary reversion from invasive to less invasive placental types (Crespi and Semeniuk 2004; Wildman et al. 2006; Hannibal et al. 2014); and (5) the observation from many viviparous species that offspring size is governed in part by offspring genotype and is not solely under maternal control (Furness et al. 2015).

With respect to this last example, perhaps most convincing is the observation of *genomic imprinting* of genes expressed in the eutherian placenta, many of which are involved in nutrient transfer across the maternofetal interface (Frost et al. 2010; Monk 2015). Genomic imprinting is characterized by monoallelic, parent-of-origin gene expression, which is mediated by various epigenetic mechanisms acting both prior to and after fertilization (Peters 2014). In vertebrates, it occurs in therian mammals (marsupials and eutherian mammals) and is apparently absent in the oviparous monotremes (Renfree et al. 2009). Little more than a hundred genes are imprinted in humans, and many are associated with disease due to monoallelic expression or disruption of imprinting itself, implying strong countervailing selection (Peters 2014; Furness et al. 2015; Wilkins et al. 2016). Importantly, many imprinted loci are expressed early in development in tissues that are involved in nutrient transfer to developing offspring, and thus regulate growth (Babak et al. 2015; Wilkins et al. 2016). Numerous studies have demonstrated that paternally expressed alleles tend to promote fetal growth or other traits that promote maternal resource transfer, whereas maternally expressed alleles tend to inhibit growth (Furness et al. 2015; Wilkins et al. 2016). Interestingly, more genes are imprinted paternally than maternally, and in adult tissues, tend to be mostly expressed in the central nervous tissues, some of which affect maternal and social

behaviors (Peters 2014; Furness et al. 2015). These patterns are consistent with the view of genomic imprinting as a form of genomic conflict (Wilkins et al. 2016). Alternative views, such as *co-adaptation theory*, hold that genomic imprinting coordinates the extraordinary complexity of sexual reproduction and fetal development between maternal, paternal, and fetal genomes (Wolf and Hager 2006).

The importance of genomic imprinting in pregnancy and early development bolsters the view that birth timing is a delicately balanced compromise between genetic elements with competing strategic interests (Crespi 2010). In this tug-of-war view of pregnancy, the genomic background out of which birth timing emerges has the potential to greatly exacerbate the effects of environmental variation.

Conclusion

PTB is among the most serious and least understood challenges facing infant and adolescent health globally. Because of the singular complexity of pregnancy (Eidem et al. 2017), identifying the causes and remedies to PTB will require concerted efforts and close collaborations between scientists form diverse fields. The diverse perspectives offered by clinical, epidemiological, sociological, and evolutionary studies all shed light on the mysteries of human pregnancy, but it is evident that much more cross-talk will be required to understand the genetic and phenotypic causes of prematurity. A fundamental challenge will be developing opportunities for scientists from diverse fields to share perspectives, not all of which will have immediate clinical relevance.

Cross-References

- ▶ Birthing Complications
- ▶ Evolution of Live-Birth in Mammals
- ▶ Implications for Pregnancy
- ▶ Low Birthweight and Preterm Infants
- ▶ Maternal-Fetal Conflict
- ▶ Narrowing Birth Canal
- ▶ Parent-Offspring Conflict
- ▶ Prenatal Environment, The

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