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Is Postpartum Hemorrhage a Legacy of our Evolutionary Past?

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INTRODUCTION

From an evolutionary perspective, postpartum hemorrhage (PPH) is an enigma: why is something with such a high risk of death so common? This chapter suggests that the increased risk of PPH in humans compared with non-human primates is an unfortunate side-effect of natural selection for larger brains. The complementary increase in neonatal brain size over the course of human evolution was enabled by the extremely invasive pattern of human placentation, which led to an increase in complications of placental separation from the uterine wall at delivery.

Each year, approximately 350,000 maternal deaths occur worldwide. The majority take place in developing countries[1]. Worldwide, one woman in 74 will die of maternal causes; in sub-Saharan Africa, however, the risk of maternal mortality can be as high as one in six[2]. Estimates from historical data and religious groups that decline medical treatment suggest that without intervention maternal mortality rates (MMRs) would be very high, perhaps 1000–1500 maternal deaths per 100,000 live births[3]. This rate approximates the current MMR in the sub-Saharan countries with the highest rates of maternal mortality, i.e. Chad, Malawi and the Central African Republic (n = 1065, 1140 and 1570, respectively)[1]. Because medical interventions such as cesarean sections are a relatively recent development in the course of human history, MMRs have very likely been as high or higher in the past.

The high rate of maternal mortality in humans stems in part from two unique human adaptations: bipedalism, which emerged at the origin of the human lineage around 7 million years ago; and enlarged brains, first seen at the emergence of our genus, *Homo*, around 2 million years ago. The development of bipedalism is thought to have allowed the earliest humans to respond to climate (and therefore habitat) change by permitting more efficient terrestrial locomotion, improved evaporative heat loss, and/or the ability to carry objects while traveling. Anatomically, however, the adoption of bipedal locomotion involved numerous changes to the bony pelvis, including the lateral widening of the pelvic girdle, a feature which led to significant shifts in the mechanism of birth[4–6]. In monkeys, the long axes of the inlet, midplane and outlet of the birth canal line up in the anterior–posterior dimension, thereby allowing the widest portion of the neonatal skull (also the anterior–posterior dimension) to navigate the birth canal without rotation, despite a relatively close correspondence between the maternal pelvic dimensions and neonatal head size[4–6]. In contrast, due to the changes in the human pelvic dimensions secondary to bipedalism, the long axes of the inlet and outlet of the modern human pelvis are perpendicular[4–6]. To navigate the tortuous birth canal, the human neonate rotates twice, once to accommodate aligning the widest portion of the fetal skull with the widest dimensions of the maternal pelvis and again so the shoulders can follow, a pattern that is thought to have originated relatively early in human history[5,6]. The process of human birth became even riskier when brain size began to enlarge dramatically with the origin of the genus *Homo* around 2 million years ago. The timing of this dramatic encephalization approximately coincided with the further narrowing of the obstetric dimensions of the pelvis, an adaptation that is thought to have greatly increased the efficiency of bipedal locomotion. The resulting incompatibility between the size and shape of the bipedal pelvis and the enlarged fetal brain, also known as cephalopelvic disproportion, is an important factor in explaining the prevalence of obstructed labor in modern humans, which accounts for 8% of maternal mortality[4,5,7].

The leading cause of maternal mortality worldwide is PPH, accounting for up to 35% of maternal deaths[8]. PPH is estimated to affect 10.5% of human births worldwide[9], but, despite its ubiquity, the underlying reasons why humans are so vulnerable to this condition remain unclear. From an evolutionary perspective, PPH is an enigma: why is something with such a high risk of death so common? Most disorders with high mortality risks are uncommon, such as Tay-Sachs disease, or more common after the completion of reproduction, as is the case with many cancers. An evolutionary approach to answering this question may therefore offer a fresh perspective on the ultimate causes of PPH in humans and, thus, on the costs and the benefits of specific features of human anatomy and physiology.

This chapter explores a novel, evolutionarily driven hypothesis regarding PPH, arguing that as adult (and therefore fetal) brain and body size increased over the course of human evolution, existing primate patterns of invasive placentation were modified to allow for increased maternal nutrient transfer *in utero*[10,11]. Unfortunately, the resultant pattern of placentation came at an unfortunate cost: uteroplacental separation at birth is more likely to be hindered, thereby leading to high rates of PPH. To support these arguments, this chapter discusses some of the key features of invasive human placentation, reviews suggestions that overly aggressive placental invasion may be critical to the etiology of PPH, and examines the comparative evidence for placental disorders related to trophoblast invasion. The chapter concludes with a consideration of the causes, timing and effects of PPH over the course of human evolution.

THE INVASIVE PATTERN OF HUMAN PLACENTATION

The existing pattern of human placentation has recently been argued to be a modification of existing patterns of primate placentation to increase nutrient transport *in utero* and support the increase in fetal brain size over time. A brief description of the development and functional morphology of the placenta is thus central to this argument[12–17]. The primate placenta forms within a few days of fertilization from trophoblastic cells of fetal origin. The trophoblasts comprise the outer cell mass (OCM) of the early blastocyst, a hollow ball of cells derived from the fertilized egg[12,13], while the inner cell mass of the blastocyst gives rise to the fetus. Because of its shared origin with the fetus, the placenta can be viewed as an extrasomatic fetal organ, which acts as a sensor of nutrient availability in the maternal circulation and thus a calibrator of fetal growth[18].

Placentas show striking variations in invasiveness, exhibiting three main phenotypes[19]. The *epitheliochorial* placenta, found in ruminants, horses and swine, is the least invasive form; it adheres to the epithelial lining of the uterine wall without penetrating it, thereby providing no contact with the underlying maternal vasculature. Nutrient transport into the fetal circulation occurs via diffusion through several layers of tissue: the walls of the maternal vessels, the surrounding endometrial stroma, the uterine epithelium and finally the chorion, which is comprised of trophoblasts from the OCM and of fetal mesoderm, a tissue deriving from one of the main three cell layers of the early embryo. In order of invasiveness, the next mode is *endotheliochorial* (as seen in dogs and cats), whereby the chorion penetrates the endometrial surface and is in contact with the endothelium of maternal vessels but is not immediately adjacent to maternal blood. The most invasive placental form is the *hemochorial* placenta (as seen in rodents and primates), in which the chorion penetrates the endometrial epithelium and the deeper endometrial stroma to arrive in direct contact with maternal vessels, the walls of which are subsequently penetrated, so that placental tissue is in direct contact with maternal blood.

Further differentiation occurs within hemochorial placentation in terms of depth of implantation. In monkeys, implantation is superficial, with only moderate penetration of the uterine wall by the chorion[17]. Trophoblast cells surround maternal vessels within the endometrium and cause them to lose some of their muscularity, which, in turn, lowers vascular resistance and increases blood flow to the developing embryo[20]. The monkey placenta thus forms a trophoblast shell, which is a mostly continuous layer of trophoblast cells within the endometrium that largely limits trophoblast invasion into the myometrium[21,22]. In contrast, the human placenta is much more invasive, lacking a trophoblast shell and deeply penetrating the uterine epithelium, even migrating through the endometrial stroma beneath into the upper third of the myometrium in a process called interstitial implantation[13,23,24]. The human trophoblasts extensively remodel the maternal spiral arterioles to nourish the rich endometrium[25]. Less is known about placentation in the other hominoids than in modern humans, but recent reports suggest that more invasive interstitial placentation also occurs in the African great apes, although the currently available data are drawn from only two chimpanzee placentas[26].

To accomplish the extraordinary feat of deeply invading the uterus and remodeling its vessels, trophoblast cells develop an invasive phenotype (Figure 1). Some become the villous cytotrophoblasts (VCT) that cover mesoderm cores to become the chorionic villi. These villi are in direct contact with maternal blood pulsating throughout the placenta. As gestation progresses, most of the cytotrophoblasts fuse to form a continuous multinucleated layer called the syncytiotrophoblast (SCT), across which nutrient, gas and waste transport takes place. Other trophoblast cells mediate the placental adherence to the uterine wall as

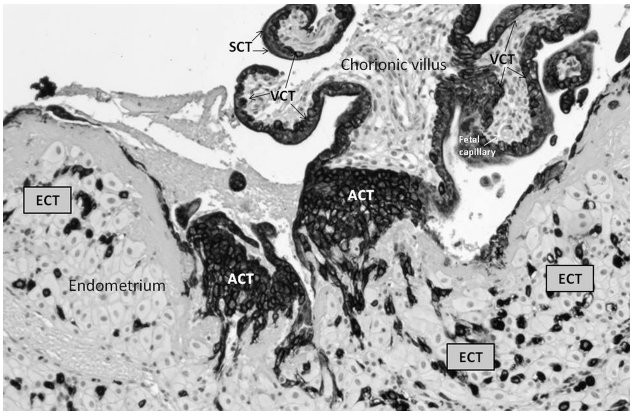

Figure 1 Human placenta. Section through chorionic villus (fetal mesoderm core covered in trophoblast) and underlying endometrium. Dark staining cells are various trophoblast phenotypes: SCT, syncytiotrophoblast; VCT, villous cytotrophoblast; ACT, anchoring cytotrophoblast; ECT, extravillous invasive cytotrophoblast. Courtesy of Harvey Kliman, MD, PhD, Yale University

anchoring columns (ACT)[27]. A final group of cytotrophoblast cells develops a highly invasive phenotype. These extravillous invasive cytotrophoblasts break free from the other trophoblast cells and migrate deeper into the uterus. They surround the maternal spiral arterioles and initiate a breakdown of their internal muscular layer (the tunica media) (Figure 2). This replaces the muscular and elastic tissue of the arteriole wall with a thick layer of non-contractile fibrinoid material, which in turn reduces vascular resistance. The shape of the vessel is also converted in such a way that its diameter increases, while its distal portion opens into a funnel-like outlet into the growing placenta[28,29]. Such changes combine to maximize blood flow, increase hemodynamic efficiency, and reduce the potential impact of vasoconstrictors[28]. The invasion and subsequent conversion of the deeper vessels of the human uterus takes place early in the second trimester, around 15 weeks[30]. In summary, these transformations increase maternal syncytiotrophoblast surface area and render maternal vasculature relatively powerless to limit physically blood flow to the placenta; these strategies channel large quantities of nutrients and oxygen to the large-for-maternal-body-size newborns of hominoids, including humans[31–34].

THE LINK BETWEEN PLACENTATION AND POSTPARTUM HEMORRHAGE

The processes of trophoblast differentiation, invasion and vascular conversion are normal components of human gestation, but all carry potentially significant risks. Pre-eclampsia, characterized by shallow trophoblast invasion and insufficient remodeling of maternal vessels, is a prime example of the disruption of the delicate balance *in utero*. In pre-eclampsia, rather than being transformed into the wide, straight funnels that easily conduct maternal blood to the placenta and in turn the fetus, the maternal spiral arterioles remain coiled, their muscular walls intact and operable, thus restricting blood flow to the placenta[35]. The resultant placental insufficiency may induce symptoms that include hypertension, proteinuria and renal pathologies, and, in the case of eclampsia, convulsions and death. Pre-eclampsia has been frequently described as a disorder unique to humans because of the role of trophoblast invasion and vascular remodeling[36–39]. Carter and Martin[40] recently critiqued the conventional thinking of pre-eclampsia being a uniquely human condition, suggesting that this assumption has not been exposed to extensive inquiry. They cite examples of physiological changes in pregnant primates that may indicate a deeper evolutionary timeline for pre-eclampsia. For example, in a study of five pregnant baboons who underwent uterine artery ligation (a treatment that effectively limits blood flow to the placenta and increases maternal blood pressure), symptoms consistent with pre-eclampsia were observed, namely, changes to the microscopic kidney morphology, proteinuria and increased blood pressure[41]. Hennessy *et al.*[42] described similar renal and hypertensive symptoms in a baboon pregnant with twins. Comparable changes to the kidney were reported in a single chimpanzee[43], and symptoms tentatively described as eclamptic convulsions were reported in two matrilineally related gorillas[44].

Although this small dataset ($n = 9$ across three genera) points to the possibility that pre-eclamptic symptoms may not be limited to humans, none of these studies described any morphological features of the placenta corresponding to the well described alteration of invasive events that characterizes pre-eclampsia in humans[35]. What is consistent in these examples, however, is the induction of a hypertensive environment, either through the mechanical restriction of blood flow to the uterus or via the demands of multiple pregnancy. Further, as Carter and Martin also note, the invasive extravillous trophoblasts responsible for the extensive remodeling of the human uterine vasculature appear to be absent in baboons and macaques, the monkey species in which placentation has been most studied[40]. Taken together, the available observations suggest that while the *hypertensive* symptoms of pre-eclampsia may be inducible within the primate order, the underlying placental causation – blocking of the characteristically deep invasion and extensive vascular remodeling – is unique to humans, or at least has not yet been definitively shown to be a component of the etiology of gestational hypertension in non-human primates.

In addition to pre-eclampsia, a number of disorders in humans represent the range of placental invasiveness. At one end of the spectrum is placental abruption, in which the placenta prematurely separates from the uterine wall, suggestive of shallow implantation[45]. On the other is the cluster of highly invasive disorders comprising placental accreta, whereby trophoblast invasion is severely dysregulated and the placenta implants far beyond its normal limits[46]. The most invasive of these is placenta percreta, in which the placenta completely penetrates the myometrium,

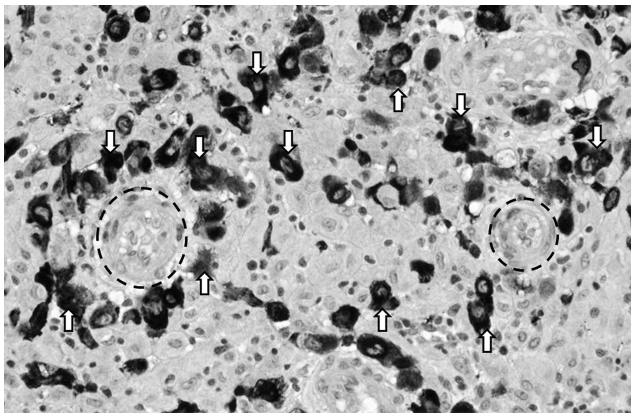

Figure 2 Darkly staining invasive extravillous cytotrophoblasts (ECT, some indicated by white arrows) surrounding maternal uterine arterioles (outlined in dashed black circles). Arteriole on the left is completely surrounded by ECT and further along the conversion process than the arteriole on the right. Courtesy of Harvey Kliman, MD, PhD, Yale University

in some cases migrating out onto organs outside the reproductive tract, such as the rectum or kidneys[47]. Placenta percreta, which can lead to spontaneous uterine rupture[48], is often localized to areas of prior uterine scarring, as the non-vascular fibrous scar tissue that replaces the muscle may allow overimplantation[49]. The highly invasive nature of human trophoblasts can also give rise to gestational trophoblastic diseases such as choriocarcinoma, a neoplasm that can metastasize to the lungs and cause death years after pregnancy[50,51].

Just as pre-eclampsia is a gestational disorder arising from impaired placentation and the resultant under-remodeling of uterine vasculature, PPH may have its roots in overly aggressive placental invasion and vascular remodeling[10]. In support of this hypothesis (and in direct contrast to pre-eclampsia), one of the clinical risk factors for PPH is macrosomia[52], which is suggestive of a high rate of nutrient delivery to the fetus, as would be expected if the vessels supplying the placenta were expanded in size, number, or power. A number of factors may contribute to this over-remodeling. For example, the maternal immune system could respond inadequately to counter the activity of invasive trophoblasts on the arterioles, leaving these vessels vulnerable to excessive remodeling and therefore overly conductive of maternal blood to the fetoplacental unit[51]. Alternatively or concomitantly, more arterioles than usual may be remodeled or even recruited to form *de novo* by the invasive cells. Indeed, invasive trophoblast cells are capable of attracting and increasing neighboring maternal blood flow through the production of factors that promote vessel dilation and discourage clot formation[53–55]. These invasive cells can also completely displace the maternal cells lining the remodeled vessels, essentially forming new blood vessels of placental origin within the uterus[55]. In addition to the great advantage of directly soliciting and facilitating increased maternal blood flow to the placenta and fetus, these mechanisms, when unchecked, may also have the effect of replacing or handicapping uterine muscle cells, thus diminishing the effective ratio of contractile to non-contractile tissue in the myometrium and dampening the ability of the uterus to contract immediately postpartum. In addition, a high rate of vascular turnover and inflammation could be accompanied by an accumulation of subclinical uterine trauma and scarring, which could also hamper contractility when it is urgently needed.

What has been laid forth above strongly suggests that the human pattern of trophoblast invasion and/or the extensive vascular remodeling of the uterus may impede the normal processes of myometrial contraction and clot formation after delivery. In a typical delivery, the placenta begins to separate from the uterine wall even before the delivery of the baby[49]. Any resulting uterine bleeding at the site of placental separation is normally stopped by 'the mechanical constriction of the blood vessels due to the uterine muscle contraction and retraction and by clots sealing off the raw surface in the placental bed'[56]. When uterine bleeding during labor or immediately after the delivery is not stopped by these mechanisms, the threat of maternal death from catastrophic hemorrhage is very real. The two major risk factors for PPH, uterine atony and a prolonged third phase of labor, together account for 93% of PPH-related deaths[57]. Uterine atony, the absence of adequate uterine contractions to sufficiently clamp the uterine vessels and stop bleeding from the 20 cm diameter wound that remains on the uterine wall when the placenta does separate, is the leading risk factor for PPH, accounting for 70% of the cases[49]. The underlying causes of uterine atony, however, are unclear. Uterine atony is often associated with retained or incomplete placenta delivery[49], but the directionality of this link is not clear. It is possible that a retained placenta and its vascular attachments may present a physical barrier to uterine muscle contraction. Conversely, uterine atony could hinder placental separation and expulsion. In addition to the physical and physiological factors that may interfere with uterine contraction, risk factors that overstretch the uterus, including multiple pregnancy, macrosomia and polyhydramnios, are also associated with atony[49]. Considering the importance of reproduction to the process of evolution by natural selection, the integration of clinical medicine and evolutionary biology is a logical avenue to pursue, despite our incomplete knowledge of the ultimate causes of PPH.

HUMAN VULNERABILITY TO POSTPARTUM HEMORRHAGE IN AN EVOLUTIONARY CONTEXT

PPH is rare in domestic animals for which data are available[58]. Noakes *et al.* report that because many domesticated animals (e.g. swine, horses, cattle) have non-invasive epitheliochorial placentas, bleeding at the time of delivery is only likely if excessive force is used to deliver the placenta[59]. In these animals, trauma followed by hemorrhage is paramount: 'the usual cause of serious hemorrhage is laceration of a uterine blood vessel by a fetal appendage, obstetric instrument, or hand of the obstetrician'[58]. In fact, Rooney[58] reports ten fatal cases of PPH in aging mares, all related to lacerations of arteries. In carnivores such as the house cat, moderately invasive endotheliochorial placentas allow for an increased risk of blood loss at delivery, which often occurs when the placenta is precipitously removed during cesarean sections[58]. These data, albeit minimal, suggest that blood loss at delivery has a direct connection to the degree of placental invasiveness, such that animals with minimally invasive epitheliochorial placentas are unlikely to bleed at delivery except in the case of induced vascular trauma, whereas those with moderately invasive endotheliochorial placentas may bleed if the placenta is prematurely separated from the uterine wall.

If indeed broad categories of placental invasiveness predict the probability and/or volume of blood loss at delivery, then primates with hemochorial placentation, which involves remodeling of at least the endometrial vasculature, should be expected to lose a small volume of blood postpartum. Unfortunately,

data available on postpartum bleeding or its risk factors in non-human primates are scant at best, save two published reports of retained placenta[60,61]. At the same time, however, few other primates approach the extreme level of cephalopelvic disproportion exhibited by humans, indicating that overall, labor in non-human primates is a simpler, less potentially traumatic event. Considering the importance of pregnancy and labor in zoos as well as captive research and breeding facilities, the lack of an anecdotal literature on PPH in non-human primates can be viewed as tentative support for the hypothesis that the elevated incidence of PPH is unique to humans, although more systematic study is clearly required, particularly among the great apes.

If PPH is not a common feature of mammalian or even primate pregnancy, when did this vulnerability arise in human history? Rockwell *et al*. suggest that the shift toward bipedal locomotion approximately seven million years ago and its attendant consequences for pelvic anatomy may have spurred changes in patterns of placental invasiveness and vascular remodeling to counteract gravitational effects[29]. A shift to habitually erect posture and bipedal locomotion places the major abdominal vasculature (e.g. abdominal aorta, inferior vena cava) at risk of compression by the gravid uterus[62]. This in turn constrains blood flow and thus oxygen to the uteroplacental unit, with potentially deleterious consequences for the developing fetus. In response, the human placenta could have modified the pre-existing primate pattern of placentation, implanting even more extensively into the myometrium and actively altering the maternal vasculature to improve placental perfusion, thereby protecting the fetus from the vascular effects of gravity[29]. Because increases in invasiveness expand the placental surface area available for transport of nutrients from the maternal to the fetal circulation[63,64], it is reasonable to suggest that changes in placental anatomy allowed an increase in intrauterine nutrition for the developing hominin fetus[11].

INCREASED FETAL NUTRIENT REQUIREMENTS IN THE GENUS *HOMO*

The origin of the genus *Homo* around 2 million years ago was marked by a number of key changes in hominin morphology, the most significant of which, from an energetic standpoint, were a significant increase in body size and a tripling of brain size, from approximately 400 cc in the earliest human ancestors to approximately 1400 cc in modern humans. This latter volume is three times larger than would be expected for a commensurately sized great ape[33,34]. Such shifts in adult body proportions would have also been associated with similar shifts in offspring proportions, such that energetic investment in fetuses and neonates in the genus *Homo* would have increased substantially as well. Modern human infants are the largest of all primate neonates[65], even though humans are not the largest primates. Corrected for maternal body size, the relationship of neonatal mass to maternal mass is still larger in humans than in almost all other primates[32–34]. Modeling by DeSilva and Lesnik[66] suggests that neonatal brain size increased 25–50% from australopithecines (~180 cc) 3 million years ago to members of the genus *Homo* (~225–270 cc) 2 million years ago. If the cost of fetal brain metabolism approximates that of the neonatal period (60–74% of energy intake compared to 20% in the adult)[33,67], then increases in absolute neonatal brain size and metabolism meant increases in the amount of energy needed during pregnancy to support a fetus. Furthermore, modern human newborns appear to be fatter than most other mammalian newborns, with the exception of guinea pigs and some aquatic mammals[32,68,69]. It is highly likely that significant changes in dietary quality, most probably increases in animal product intake (e.g. meat) relative to other foods, accompanied the origin of the genus *Homo*[70–72]. Taken together, the enhanced metabolic requirements of pregnancy due to increased human neonatal weight, adiposity and especially brain size suggest that the origin of the genus *Homo* was accompanied by a significant increase in the energetic cost of bringing a fetus to term[11].

Skeletal anatomy related to habitual bipedalism applies a constraint on this investment and resultant *in utero* brain growth, in that it 'determines rigidity and arrangement of the bones in the pelvis, affects the size of the birth canal, and thus determines the maximum fetal size at birth'[7]. A number of human adaptations maximize the deliverable neonatal head size, including an expandable pubic symphysis[73,74] and compressible fetal skull[75]. In addition, traditional labor positions, such as squatting, take advantage of gravity and allow the pelvis to open to its maximum width[7]. Furthermore, the uniquely human pattern of assistance during labor permits manual rotation and/or maneuvering of the fetus during parturition[7].

Human parturition occurs at the point beyond which fetal and potentially maternal demise would be far too likely to be favored by selection, as too large a fetal head simply would not be able to exit the pelvis. As a result of this constraint, the human fetus has often been characterized as being born at a far more immature developmental stage than the other primates[33,76,77], yet nonetheless it has the biggest absolute brain size. The large size of the human neonatal brain relative to maternal mass[78] suggests that additional energy is being channeled to the fetus.

In particular, maternal fatty acids such as docosahexaenoic acid (DHA) are key nutrients for intrauterine and postnatal brain development[71,79], especially for the production of myelin, the fatty sheath encasing axons and enhancing cognitive function. The fatty acid concentration in placental circulation is dependent on two main factors: the maternal concentration of fatty acids and their efficient transfer across the placenta[80,81]. Although long chain polyunsaturated fatty acids (LCPUFA) can be transported passively across the maternal–fetal concentration gradient, recent research emphasizes the importance of plasma membrane-located transport/binding proteins in this process[82,83]. The transport proteins existing on

the placental interface are saturable, so that the rate of LCPUFA transport is maximized when all the binding sites are filled. Because the rates of both passive transport by diffusion, which is directly correlated to surface area, and active transport via transport proteins, which increases in number as the area of the membrane increases, are related to surface area, increased placental surface area might thus allow for increased transfer of fatty acids across the placenta. An expansion of placental surface area would be one way to increase the efficiency of intrauterine nutrient transport in hominins without the need for qualitatively altering caloric intake relative to other primates. Rutherford and Tardif demonstrated that the placentas of marmoset monkey triplet litters had a significantly expanded transport surface area compared with those of twin litters, despite a reduction in the ratio of maternal to fetal mass, suggesting that increasing the area available for transport is an efficient strategy to support greater fetal growth in primates[84]. Taken together with the hypothesized shifts in early hominin diets to include more animal products[70,71], which in turn would be expected to increase maternal fatty acid and ketone concentrations[85] and thus the supply available to the developing fetus, increases in placental fatty acid transport to the fetus were very likely critical to the evolutionary trajectory of hominin brain development. It has been proposed recently that without changes in hominin placentation that both intensify invasion into the uterine wall and expand the surface area in contact with maternal blood, combined with changes in diet quality, growing a large and highly myelinized fetal brain would have represented so large a portion of maternal energy expenditure as to render increases in fetal brain growth prohibitively costly, aside from any mechanical constraints of the abdominal and pelvic anatomy on parturition[11].

EVIDENCE FOR THE LONGSTANDING HISTORY OF POSTPARTUM HEMORRHAGE IN HUMANS

Genetic and ethnographic evidence offer more clues to a longstanding human history of PPH. Lindqvist and colleagues[86,87] argue that thrombophilias, polymorphisms that promote coagulation, have been selected for their ability to counterbalance the risk of PPH. Factor V Leiden (FVL), one of the best characterized procoagulatory mutations, causes a resistance to the anticoagulatory activity of activated protein C (APC)[88], which allows individuals with the FVL mutation to clot faster. Approximately 5% of Europeans carry the FVL gene, and frequencies can reach as high as 10–15% in northern Europe, where the mutation likely arose[88] approximately 21,000 years ago[89]. In a retrospective Swedish study, Lindqvist *et al.* found that women who were homozygous or heterozygous for the FVL mutation lost significantly less blood at delivery (an average of 60 ml less blood lost; $p = 0.001$) and were significantly less likely to hemorrhage than individuals without the mutation (defined in this study as 600 ml blood loss or more; 2% of those with the mutation versus 14% of those without it; $p = 0.01$)[86]. Even if thrombophilias offer protection against PPH, carriers may incur other potentially significant costs. The most significant of these costs is an increased risk of thromboembolism in pregnancy, which accounts for approximately 15% of maternal deaths[8]. A recent systematic literature review and meta-analysis of the risk of thrombosis in pregnancy for FVL carriers determined that homozygotes have a relative risk as high as 34.4% compared with the 8.3% risk of heterozygotes, although this does not translate to an exceptionally high absolute risk (3.4% in homozygotes and 0.8% in heterozygotes), given the rarity of thrombosis in the overall population (1:1000)[90]. The costs of FVL, which accounts for over 40% of all thromboses, are also suggested by its virtual absence among natives of Africa and Asia[88], parts of the world where the mortality rate due to PPH is especially high. Lindqvist and colleagues[86,87] argue that the maintenance of the FVL allele at such a high frequency despite its associated risks is indicative of strong balancing selection for protection against PPH.

In addition to genetic factors, humans have developed multiple behavioral interventions for PPH and its risk factors. Lefèber and Voorhoeve extensively reviewed child birth customs and discussed a number of interventions used by traditional birth attendants (TBAs) that appear to replicate the effects of active management of the third phase of labor[91]. First, if the placenta is delayed, TBAs may administer substances or perform actions that will cause the delivering woman to sneeze, gag, or vomit, thus tensing her abdominal muscles and potentially contracting the uterus. For example, TBAs may insert garlic or hair into the woman's mouth or administer salted water to induce gagging or vomiting[91]. In Jamaica, the woman may be encouraged to inhale deeply followed by exhaling forcefully into a bottle; this maneuver applies internal pressure to the uterus and can stimulate contractions[92]. Second, abdominal pressure and uterine massage, pressing and rubbing are widely reported[91]. In West Melanesia, a hot compress made of wood may be applied to the vulva and abdomen to stop the flow of blood[93]. Third, while it is not precisely 'controlled cord traction', Lefèber and Voorhoeve present examples from India, Malaysia, Ghana and Indonesia of TBAs pulling on the umbilical cord and manually removing the placenta[91]. Such examples demonstrate that TBAs may attend to cues of possible PPH and possibly intervene in manners that may replicate WHO's mechanisms of active management of the third phase of labor. The cross-cultural variations in these interventions suggest these traditions have longstanding cultural roots, and the minimal materials required suggest that these sorts of interventions could have been performed by earlier hominins[94].

CONCLUSION

PPH is the leading cause of maternal mortality worldwide. The condition exacts huge tolls on human

capital, particularly where women do not have ready access to medical care. Research on PPH traditionally has focused on treatments and risk factors, whereas comparatively little work has been performed to explore the underlying mechanisms of this potentially fatal disorder. As argued here, the high risk of PPH-related mortality in humans is potentially a consequence of placental adaptations toward intense invasiveness and radical remodeling of maternal vasculature, driven by the energetic demands of the large-bodied and large-brained hominin fetus. However, the transformative activity of the human trophoblast cells carries with it significant risk of gestational complications for both mother and offspring. The example of pre-eclampsia – a serious hypertensive complication of pregnancy caused by inadequate vascular remodeling of the uteroplacental unit – serves as a corollary for the etiology of PPH reviewed here and illustrates the delicate balance between investment and risk. If adequate uterine vascular remodeling is not achieved, then the mother is placed at risk of hypertension and death, and the fetus may experience growth restriction and its cascade of lifelong health consequences. If the target of vascular remodeling is exceeded, on the other hand, the resultant excessive remodeling, hyperperfusion of the placenta, and over nourishment of the fetus, may lead to catastrophic maternal bleeding and maternal and fetal death.

Although the human placenta shares deep phylogenetic roots with the primate hemochorial placenta, the morphology of the modern human placenta appears to be distinct from that of other primates, as indicated by available histological and physiological studies of the placenta, comparative data on pregnancy outcomes, and the time depth of PPH suggested by coagulation factor polymorphism distribution and ethnographic consilience in birth practices[10,11]. Because more than 50% of PPH cases currently have no identifiable risk factors[95], understanding the underlying cause of the increased risk of PPH in humans is an important step toward discovering new modes of treatment and eventually prevention on a global scale. Interdisciplinary collaborations based on an understanding of the evolutionary biology and physiological mechanisms of placentation and uterine vascular remodeling may hold the best hope for aiding women and health care providers to make evidence-based, pragmatic choices about place of delivery.

PRACTICE POINTS

- The pattern of human placentation is highly invasive, which is likely an adaptation to support intense brain growth *in utero*
- The deeply invasive nature of the human placenta may impede the process of uteroplacental separation at birth, thereby leading to high rates of PPH
- Based on available data, the frequency of PPH in humans is much higher than in our closest relatives, the non-human primates, which generally have less invasive placentas and less brain growth *in utero*
- The high prevalence of PPH in humans may have begun 2 million years ago, when human brain size expanded; this longstanding history is reflected in genetic and cultural adaptations to PPH.

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References

1. Hogan MC, Foreman KJ, Naghavi M, et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet 2010;375:1609–23
2. Ronsmans C, Graham WJ. Maternal mortality: who, when, where, and why. Lancet 2006;368:1189–200
3. Van Lerberghe W, De Brouwere V. Of blind alleys and things that have worked: History's lessons on reducing maternal mortality. Stud Health Serv Org Policy 2001;17:7–34
4. Rosenberg K. The evolution of modern human childbirth. Yearbook Physical Anthropol 1992;35:89–124
5. Rosenberg K, Trevathan W. Bipedalism and human birth: the obstetrical dilemma revisited. Evol Anthropol 1996;4: 161–8
6. Rosenberg K, Trevathan W. Birth, obstetrics and human evolution. Br J Obstet Gynaecol 2002;109:1199–206
7. Trevathan W. Human Birth: An Evolutionary Perspective. New York, NY: Aldine de Gruyter, 1987
8. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: A systematic review. Lancet 2006;367:1066–74
9. WHO. The World health report: 2005: make every mother and child count. Geneva, Switzerland: World Health Organization, 2005

10. Abrams E, Rutherford J. Framing postpartum hemorrhage as a consequence of human placental biology: an evolutionary and comparative perspective. Am Anthropol 2011;113: 417–30
11. Rutherford J, Abrams E, Said SJ. Developing the brain: a potential role for the placenta in hominin brain evolution. American Association of Physical Anthropologists, Portland, OR, Oral Presentation, 13 April 2012
12. Mossman HW. Comparative morphogenesis of the fetal membranes and accessory uterine structures. Carnegie Inst Contrib Embryol 1937;26:129–246
13. Mossman HW. Vertebrate Fetal Membranes. New Brunswick, NJ: Rutgers University Press, 1987
14. Luckett WP. Comparative development and evolution of the placenta in primates. Contrib Primatol 1974;3:142–234
15. Wislocki GB. On the placentation of primates, with a consideration of the phylogeny of the placenta. Contrib Embryol 1929;20:51–80
16. Benirshcke K, Kaufmann P. Anatomical and functional differences in the placenta of primates. Biol Reprod 1982;26:29–53
17. Luckett WP. Cladistic relationships among primate higher categories: evidence of the fetal membranes and placenta. Folia Primatol (Basel) 1976;25:245–76
18. Jansson T, Powell TL. IFPA 2005 Award in Placentology Lecture. Human placental transport in altered fetal growth: does the placenta function as a nutrient sensor? — a review. Placenta 2006;27 (Suppl A):S91–7
19. Grosser O. Vergleichende Anatomie und Entwicklungsgeschichte der Eihäute und der Placenta. Vienna, Austria: Wilhelm Braumüller, 1909
20. Kaufmann P, Black S, Huppertz B. Endovascular trophoblast invasion: implications for the pathogenesis of intrauterine growth retardation and preeclampsia. Biol Reprod 2003;69: 1–7
21. Blankenship TN, Enders AC. Modification of uterine vasculature during pregnancy in macaques. Microsc Res Tech 2003;60:390–401
22. Ramsey EM, Houston ML, Harris JW. Interactions of the trophoblast and maternal tissues in three closely related primate species. Am J Obstet Gynecol 1976;124:647–52
23. Enders AC, Lantz KC, Schlafke S. Preference of invasive cytotrophoblast for maternal vessels in early implantation in the macaque. Acta Anatomica (Basel) 1996;155:145–62
24. Pijnenborg R, D'Hooghe T, Vercruysse L, Bambra C. Evaluation of trophoblast invasion in placental bed biopsies of the baboon, with immunohistochemical localisation of cytokeratin, fibronectin, and laminin. J Med Primatol 1996;25: 272–81
25. Robillard P-Y, Dekker GA, Hulsey TC. Evolutionary adaptations to pre-eclampsia/eclampsia in humans: low fecundability rate, loss of oestrus, prohibitions of incest and systematic polyandry. Am J Reprod Immunol 2002;47: 104–11
26. Carter AM, Pijnenborg R. Evolution of invasive placentation with special reference to non-human primates. Best Pract Res Clin Obstet Gynaecol 2010;24:I1–I2
27. Kliman HJ. Uteroplacental Blood Flow: The story of decidualization, menstruation, and trophoblast invasion. Am J Pathol 2000;157:1759–68
28. Espinoza J, Romero R, Mee Kim Y, et al. Normal and abnormal transformation of the spiral arteries during pregnancy. J Perinat Med 2006;34:447–58
29. Rockwell LC, Vargas E, Moore LG. Human physiological adaptation to pregnancy: inter- and intraspecific perspectives. Am J Hum Biol 2003;15:330–41
30. Robillard P, Dekker G. Evolutionary adaptations to pre-eclampsia/eclampsia in humans: low fecundability rate, loss of oestrus, prohibitions of incest and systematic polyandry. Am J Reprod Immunol 2002;47:104–14
31. Chaline J. Increased cranial capacity in hominid evolution and preeclampsia. J Reprod Immunol 2003;59:137–52
32. Dufour DL, Sauther ML. Comparative and evolutionary dimensions of the energetics of human pregnancy and lactation. Am J Hum Biol 2002;14:584–602
33. Martin RD. Human brain evolution in an ecological context. Fifty-second James Arthur Lecture on the Evolution of the Human Brain; American Museum of Natural History, New York, 1983
34. Martin RD. Human reproduction: a comparative background for medical hypotheses. J Reprod Immunol 2003;59: 111–35
35. Fisher SJ. The placental problem: linking abnormal cytotrophoblast differentiation to the maternal symptoms of pre-eclampsia. Reprod Biol Endocrinol 2004;2:53
36. Jauniaux E, Poston L, Burton GJ. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. Hum Reprod Update 2006;12:747–55
37. Chez RA. Nonhuman primate models of toxemia of pregnancy. In: Lindheimer M, Katz A, Zuspan F, editors. Hypertension in Pregnancy. New York: John Wiley & Sons, 1976
38. Pijnenborg R, Vercruysse L, Hanssens M. The uterine spiral arteries in human pregnancy: facts and controversies. Placenta 2006;27:939–58
39. Rosenberg K, Trevathan W. An anthropological perspective on the evolutionary context of preeclampsia in humans. J Reprod Immunol 2007;76:91–7
40. Carter AM, Martin RD. Comparative anatomy and placental evolution. In: Pijnenborg R, Brosens I, Romero R, eds. Placental Bed Disorders: Basic Science and its Translation to Obstetrics. Cambridge: Cambridge University Press, 2010: 109–26
41. Makris A, Thornton C, Thompson J, et al. Uteroplacental ischemia results in proteinuric hypertension and elevated sFLT-1. Kidney Int 2007;71:977–84
42. Hennessy A, Gillin AG, Painter DM, Kirwan PJ, Thompson JF, Horvath JS. Evidence for preeclampsia in a baboon pregnancy with twins. Hypertens Preg 1997;16:223–8
43. Stout C, Lemmon WC. Glomerular capillary endothelial swelling in a pregnant chimpanzee. Am J Obstet Gynecol 1969;105:212–5
44. Thornton JG, Onwude JL. Convulsions in pregnancy in related gorillas. Am J Obstet Gynecol 1992;167:240–1
45. Tikkanen M. Etiology, clinical manifestations, and prediction of placental abruption. Acta Obstet Gynecol Scand 2010;89: 732–40
46. Angstmann T, Gard G, Harrington T, Ward E, Thomson A, Giles W. Surgical management of placenta accreta: a cohort series and suggested approach. Am J Obstet Gynecol 2010; 202:38 e1–9
47. Moore LE, Gonzalez I. Placenta percreta with bladder invasion diagnosed with sonography: images and clinical correlation. J Diagn Med Sonograph 2008;24:238–41
48. Esmans A, Gerris J, Corthout E, Verdonk P, Declercq S. Placenta percreta causing rupture of an unscarred uterus at the end of the first trimester of pregnancy: case report. Hum Reprod 2004;19:2401–3
49. Khan RU, El-Refaey H. Pathophysiology of postpartum hemorrhage and third stage of labor. In: B-Lynch C, Keith LG, Lalonde AB, Karoshi M, eds. A Textbook of Postpartum Hemorrhage. Duncow, UK: Sapiens Publishing, 2006:62–9
50. Shintaku M, Hwang MH, Amitani R. Primary choriocarcinoma of the lung manifesting as diffuse alveolar hemorrhage. Arch Pathol Lab Med 2006;130:540–3
51. Smith HO, Kohorn EI, Cole LA. Choriocarcinoma and gestational trophoblastic disease. Obstet Gynecol Clin North Am 2005;32:661–84
52. Sacks DA, Chen W. Estimating fetal weight in the management of macrosomia. Obstet Gynecol Surg 2000;55: 229–39
53. Athanassiades A, Lala PK. Role of placenta growth factor (PIGF) in human extravillous trophoblast proliferation, migration and invasiveness. Placenta 1998;19:465–73

54. Cross JC, Hemberger M, Lu Y, et al. Trophoblast functions, angiogenesis and remodeling of the maternal vasculature in the placenta. Mol Cell Endocrinol 2002;187:207–12
55. Hemberger M, Nozaki T, Masutani M, Cross JC. Differential expression of angiogenic and vasodilatory factors by invasive trophoblast giant cells depending on depth of invasion. Dev Dynam 2003;227:185–91
56. Choo WL, Chua S, Chong YS, et al. Correlation of change in uterine activity to blood loss in the third stage of labour. Gynecol Obstet Invest 1998;46:178–80
57. Carroli G, Cuesta C, Abalos E, Gulmezoglu AM. Epidemiology of postpartum haemorrhage: a systematic review. Best Pract Res Clin Obstet Gynaecol 2008;22:999–1012
58. Rooney JR. Internal hemorrhage related to gestation in the mare. Cornell Vet 1964;54:11–17
59. Noakes DE, Parkinson TJ, England GCW, Arthur GH. Arthur's Veterinary Reproduction and Obstetrics, 8th edn. Philadelphia, PA: WB Saunders, 2001
60. Bronson E, Deem SL, Sanchez C, Murray S. Placental retention in a golden lion tamarin (Leontopithecus rosalia). J Zoo Wildlife Med 2005;36:716–8
61. Halbwax M, Mahamba CK, Ngalula A-M, Andre C. Placental retention in a bonobo (Pan paniscus). J Med Primatol 2009;38:171–4
62. Abitbol MM. Growth of the fetus in the abdominal cavity. Am J Physic Anthropol 1993;91:367–78
63. Baur R. Morphometric data and questions concerning placental transfer. Placenta 1981;2(Suppl):S35–S44
64. Baur R. Morphometry of the placental exchange area. Adv Anat Embryol Cell Biol 1977;53:3–65
65. Smith R, Leigh S. Sexual dimorphism in primate neonatal body mass. J Hum Evol. 1998;34:173–201
66. DeSilva JM, Lesnik JJ. Brain size at birth throughout human evolution: A new method for estimating neonatal brain size in hominins. J Hum Evolut 2008;55:1064–74
67. Holliday MA. Metabolic rate and organ size during growth from infancy to maturity and during late gestation and early infancy. Pediatrics 1971;47:169
68. Kuzawa CW. Adipose tissue in human infancy and childhood: an evolutionary perspective. Yearbook Physical Anthropol 1998;41:177–209
69. Garn SM. Fat thickness and growth process during infancy. Hum Biol 1956;28:232–50
70. Aiello LC, Wheeler P. The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. Curr Anthropol 1995;36:199–221
71. Cunnane SC, Crawford MA. Survival of the fattest: fat babies were the key to evolution of the large human brain. Comp Biochem Physiol A Mol Integr Physiol 2003;136: 17–26
72. Leonard WR, Robertson ML. Evolutionary perspectives on human nutrition: The influence of brain and body size on diet and metabolism. Am J Hum Biol 1994;6:77–88
73. Putschar WGJ. The structure of the human symphysis pubis with special consideration of parturition and its sequelae. Am J Phys Anthropol 1976;45:589–94
74. Hisaw FL, Zarrow MX. The physiology of relaxin. In: Harris RS, Thimann KV, eds. Vitamins and Hormones: Advances in Research and Applications. New York: Academic Press Inc, 1951
75. Lapeer RJ, Prager RW. Fetal head moulding: finite element analysis of a fetal skull subjected to uterine pressures during the first stage of labour. J Biomechan 2001;34:1125–33
76. Dienske H. A Comparative approach to the question of why human infants develop so slowly. In: Else JG, Lee PC, eds. Primate Ontogeny, Cognition and Social Behaviour. Cambridge, UK: Cambridge University Press, 1986:145–54
77. Martin RD. The evolution of human reproduction: a primatological perspective. Am J Phys Anthropol 2007;(Suppl 45):59–84
78. Zihlman A. The natural history of apes: Life history features of females and males. In: Morbeck M, Galloway A, Zihlman A, eds. The Evolving Female A Life History Perspective. Princeton, NJ: Princeton University Press, 1997:86–103
79. Innis SM. Dietary (n-3) fatty acids and brain development. J Nutrit 2007;137:855–9
80. Cetin I, Alvino G, Cardellicchio M. Long chain fatty acids and dietary fats in fetal nutrition. J Physiol 2009;587:3441–51
81. Haggarty P, Ashton J, Joynson M, Abramovich DR, Page K. Effect of maternal polyunsaturated fatty acid concentration on transport by the human placenta. Biol Neonate 1999;75: 350–9
82. Duttaroy AK. Transport of fatty acids across the human placenta: A review. Prog Lipid Res 2009;48:52–61
83. Hanebutt FL, Demmelmair H, Schiessl B, Larque E, Koletzko B. Long-chain polyunsaturated fatty acid (LC-PUFA) transfer across the placenta. Clin Nutrit 2008;27: 685–93
84. Rutherford JN, Tardif SD. Developmental plasticity of the microscopic placental architecture in relation to litter size variation in the common marmoset monkey (Callithrix jacchus). Placenta 2009;30:105–10
85. Adam-Perrot A, Clifton FB. Low-carbohydrate diets: nutritional and physiological aspects. Obesity Rev 2006;7: 49–58
86. Lindqvist PG, Svensson PJ, Dahlback B, Marsal K. Factor V Q506 mutation (activated protein c resistance) associated with reduced intrapartum blood loss — a possible evolutionary selection mechanism. Thromb Haemost 1998;79:69–73
87. Lindqvist PG, Dahlback B. Carriership of factor V Leiden and evolutionary selection advantage. Curr Med Chem 2008;15: 1541–4
88. Spina V, Aleandri V, Morini F. The impact of the factor V Leiden mutation on pregnancy. Hum Reprod Update 2000; 6:301–6
89. Zivelin A, Mor-Cohen R, Kovalsky V, et al. Prothrombin 20210G>A is an ancestral prothrombotic mutation that occurred in whites approximately 24 000 years ago. Blood 2006;107:4666–8
90. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: a systematic review. Br J Haematol 2006;132: 171–96
91. Lefèber Y, Voorhoeve HWA. Indigeous Customs in Childbirth and Child Care. Assen, The Netherlands: Van Gorcum & Comp, 1998
92. Kitzinger S. The Social Context of Birth: Some comparisons between childbirth in Jamaica and Britain. In: MacCormack C, ed. Ethnography of Fertility and Birth. London: Academic Press, 1982
93. Kuntner L. Die Gebarhaltung der Frau. Munich: Hans Marseille Verlag, 1988
94. Lynch FG, Abrams ET. Obligate Midwifery as a Strategy to Minimize Postpartum Hemorrhage. 34th Annual Meeting of the Human Biology Association; Chicago, IL, 2009
95. Kominiarek MA. Postpartum hemorrhage. Hospital Phys Obstet Gynecol Board Rev Manual 2008;11:1–12