CHAPTER 11

Possible Role of Eclampsia/ Preeclampsia in Evolution of Human Reproduction

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Preeclampsia is the consequence of a defective implantation of the placenta that occurs during a critical developmental moment, the second phase of trophoblastic invasion when the human placenta penetrates even more deeply into the uterine wall, presumably due to the increased energy demands of the human fetus. This defect associated with the process of secondary implantation, as Robillard and his colleagues describe, is one of the major causes of intrauterine growth retardation. In an attempt to overcome this failure of implantation, pregnant women exhibit increased blood pressure (gestational hypertension), and the health of both the mother and infant is threatened throughout the rest of the pregnancy. In extreme forms, and when undetected, preeclampsia can lead to maternal seizures and epileptic convulsions (referred to as eclampsia), accounting for about 70,000 deaths of women worldwide. Robillard et al. point out that this type of hypertensive disorder of pregnancy (HDP) is mostly associated with first pregnancies and, more specifically, with women who have not sexually cohabited with their male partners for more than 4 or 5 months. Changing sex partners relatively frequently is another risk factor for preeclampsia. It seems that the longer the father has exchanged body fluids with the mother, therein exposing her to his antigens, the less likely this disease finds expression. Researchers conclude, therefore, that preeclampsia should no longer be considered "a condition of first pregnancy" but more accurately "a condition of first pregnancy *for a couple*" and, thus, a "couples disease." Robillard and colleagues propose that selection favored the loss of estrus (sexual periodicity) among evolving hominins specifically to facilitate more frequent intercourse with the same partner and, hence, longer exposure to male sperm antigens in the female reproductive tract. From an immunological and biochemical perspective, this behavior reduces the chances of the female's immune system rejecting the sperm as if they were foreign invaders, and thus reducing the chances of eclampsia/preeclampsia. In this way, Robillard integrates

changes in male–female sociosexual relationships in the hominin lineage with increasing brain size, cranial formation in utero, and loss of estrus, which altogether proposes a new explanation of a significant contemporary health challenge.

HYPERTENSIVE DISORDERS OF PREGNANCY: 10% OF HUMAN PREGNANCIES

Collectively, the different manifestations of hypertensive disorders of pregnancy (HDP) represent the main reproductive burden of human reproduction. Notably, this phenomenon does not occur in other mammals, including primates (Walker, 2000). HDP occur in approximately 10% of human births (approximately 14 million per year of the 136 million births worldwide [WHO, 1999b, 2000]).

Besides the abnormally elevated blood pressure in women with HDP, other major complications can occur, including eclampsia (maternal seizures or epileptic convulsions that could lead to cerebral injury), which represents, without medical intervention, 0.5–1% of human births (approximately 700,000 per year according to the estimates of the World Health Organization [WHO, 1999b, 2000]). More than 95% of cases occur in developing countries, and they often result in the death of the mother as well as the infant. Additionally, in 3% of human pregnancies, HDP will be complicated by generalized endothelial cell disease ("severe preeclampsia") that induces damage to the kidneys (proteinuria due to a glomeruloendotheliosis) or the liver (the HELLP syndrome—hemolysis, elevated liver enzymes, and low platelet count). Severe preeclampsia, without modern medical interventions, results, in one fourth to one third of cases, in cerebral vasculopathy and induces epileptic seizures of eclampsia. Finally, in 7% of pregnancies, women will present with "simple hypertension," which is reversible after birth. HDP is the number one cause of maternal deaths in developed countries and number three in developing areas (after bleeding and sepsis), representing approximately 70,000 maternal deaths per year worldwide out of 530,000 cases (WHO, 1999b, 2000).

The common thread linking all of the complications associated with HDP is that their only known definitive cure is delivery of the fetus and placenta by whatever means possible, including induced labor and cesarean section. As such, preeclampsia is the most common cause of medically induced prematurity. The long-term survival of these newborns depends on access to resources and knowledge of modern neonatology (Brown, 1997).

Preeclampsia is harmful to both the mother and the fetus. Because of poor maternal–fetal vascular exchange, it is the primary cause of intrauterine growth retardation (IUGR), resulting in increased numbers of babies delivered "small for gestational age," or SGA. Throughout the history of humankind, SGA newborns have paid the highest price of infant mortality (Levene, 1985).

In epidemiological terms, HDP are one of the plagues of human reproduction. There are no naturally occurring animal models of HDP and only a few isolated reports from primates including Patas monkeys (Palmer et al., 1979) and lowland gorillas (Baird, 1981). These are reports on single cases of epilepsy during delivery and seem to be

infrequent when compared to the number of human births associated with HDP. In rare cases, mammals may present epileptic seizures at delivery because of, for example, hemorrhage or hypoglycemia, but these are not the same as HDP.

Eclampsia (maternal convulsions) has been described in humans from different cultures as early as 4200 years ago (Lindheimer et al., 1999). Eclampsia was probably interpreted as a curse since epilepsy was associated in all past human cultures with possession by evil spirits. It is interesting to speculate that our ancestors may have been able to make the connection between preeclampsia and eclampsia, having observed that young women with edema (abnormal accumulation of liquid in the tissues, one of the signs of renal dysfunction) at the end of pregnancy were likely to develop eclampsia at delivery and/or produced tiny newborns.

WHY THIS REVERSIBLE HYPERTENSION DURING PREGNANCY?

Preeclampsia is the consequence of a defect in the second phase of trophoblastic invasion (Pijnenborg, 1996; Zhou, 1997). This secondary invasion as a normal part of the development of the fetus in humans is unique among mammals. The first trophoblastic invasion occurs at the time of implantation, a few days after fertilization, as in all mammals. In humans, a second invasion occurs 3 months later, after an apparent biological pause, penetrating deep (as much as one third) into the uterine wall. During preeclampsia, this second delayed implantation is incomplete (see Figure 11-1). As a result, vascular exchanges between the mother and the fetus are severely compromised for the remainder of the pregnancy. This secondary implantation failure is the major cause of human IUGR. In an effort to overcome this failure, pregnant women exhibit a

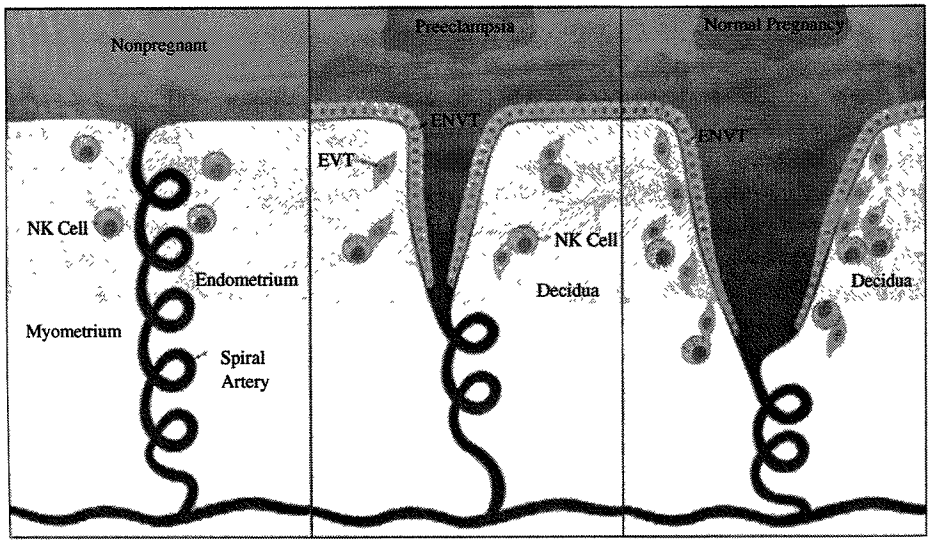

FIGURE 11-1 Endometrium in nonpregnant, preeclampsia, and normal pregnancy.

hypertensive response as a compensatory mechanism to try to provide as much nutrition to the fetus as possible.

The increased fetal nutritional needs at the end of the first trimester result in part from the increasing energy demands of the relatively large developing fetal brain, and this increased energy demand may be implicated in the need for the secondary deep trophoblastic invasion. The success of this second, deeper, penetration at 3 months of pregnancy may require a significant immunogenetic compromise in terms of paternal–maternal tissue tolerance when compared to other mammals characterized by a single trophoblastic invasion.

PREECLAMPSIA, DISEASE OF FIRST PREGNANCIES ALSO A "COUPLE DISEASE"

Complications associated with hypertension in preeclampsia and eclampsia are the result of a global endothelial disease in maternal organisms (Roberts et al., 1989). The complications are particularly likely among women with predisposition to vascular diseases (diabetes, obesity, thrombophilia). In young women (less than 25 years), however, before genetic predispositions for these diseases have been expressed, it has long been observed that HDP most commonly occurs in first pregnancies. It has been well known for three centuries that eclampsia and preeclampsia were "the disease of primigravidae" with rare recurrence in subsequent ones (Chesley, 2000). It has also been recognized for a considerable time that any kind of previous pregnancy (complete to term, spontaneous miscarriage or elective abortion) was protective against preeclampsia in successive pregnancies (MacGillivray, 1983; Seidman et al., 1989). Preeclampsia (and eclampsia) were also found to be essentially absent in primigravid women who conceived after a period of long sexual cohabitation (Marti & Herrman, 1977).

Preeclampsia and eclampsia have been also described in multigravid women with a short period of sexual cohabitation, such as multigravid women who have changed partners. In both multigravidae and primigravidae, HDP occur in approximately 40% of couples with less than 4 months of cohabitation before conception, 25% of those with 5–8 months, 15% of those with 9–12 months, and 5% of those of more than 12 months (and the same father in multigravidae) (Robillard et al., 1994, 1996). These data suggest that HDP/preeclampsia are not just conditions of mothers, but a "couple's disease" (Dekker, 1998; Dekker & Robillard, 2005; Robillard et al., 1994). Considering that HDP/preeclampsia is a disease of first pregnancy and that multiparous women with a new partner have the same risk as primiparous women, it can be concluded that it is the first pregnancy with a specific partner that is of concern. This recognition is very important, because preeclampsia is no longer viewed as a condition of first pregnancy (primiparas), but more a condition of "first pregnancy for a couple," suggesting a paternal–maternal interaction in its etiology.

Any disease that is more likely to occur in new couples conceiving very shortly after the onset of their sexual relations suggests that it is very disadvantageous for a human female to become pregnant on her first ovarian cycles with a new partner. A relatively long period of sexual cohabitation before conception (at least 6 months) is required to lessen the incidence of HDP/preeclampsia (Robillard et al., 1994). A series of nonconceptive

cycles may offer an opportunity for the maternal development of habituation to or a tolerance of paternal antigens. This is accomplished by sperm exposure, which is essentially an antigen challenge in the presence of immunosuppressive factors and tolerance promoting cytokines such as transforming growth factor beta (TGFß) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Roberson et al., 2003). This leads to immune responsiveness and later tolerance to paternal antigens, allowing the deep secondary implantation of the human trophoblast (Dekker & Robillard, 2005). The development of maternal tolerance towards paternal specific tissues reduces the risk of preeclampsia in subsequent pregnancies with the same partner. In summary, to reduce the risk of preeclampsia/eclampsia, conception in the human female should occur after an extended period of sexual cohabitation, regardless of parity of the female, if it is a first pregnancy for that couple. Interestingly, oral sex (specifically swallowing sperm) is suspected to be protective (Koelman, 2000), whereas using condoms as a regular method of contraception is a risk factor for preeclampsia (Dekker, 1998, 2005).

WHY A VERY DEEP TROPHOBLASTIC IMPLANTATION IN HUMAN PREGNANCY? EVOLUTIONARY CONSIDERATIONS

The very deep trophoblastic implantation in humans suggests that the human fetus exhibits increased nutritional needs as compared with other mammals. The source of these increased energetic demands is the human brain. The fetal human brain requires 60% of total maternal nutritional supplies in utero, compared with the 20% demand on maternal energy in utero in the majority of the 4300 other species of mammals (Cunnane et al., 1993; Martin, 1996).

CRANIO-FACIAL CONTRACTION IN PRIMATES

Since the end of the nineteenth century (Deniker, 1886) and throughout the twentieth (Anthony, 1952; Biegert, 1936, 1957; Delattre, 1952, 1958; Delattre & Fenart, 1954, 1956, 1960; Schultz, 1926, 1936, 1955, 1960), it has been noticed that one of the major evolutionary trends in primate and hominid evolution is an increase in cranial capacity simultaneously accompanied by cranio-facial contractions. The evolutionary changes in the base of the cranium were characterized by varying degrees of occipital flexion and prognathism, depending on locomotory patterns (bipedalism). Gudin (1952) pioneered a global architectural analysis in the sagittal plane, showing that flexure at the base of the skull corresponds to the face riding over the frontal bone. This morphogenetic pattern is found in many living apes and also in the evolutionary phenomenon of hominization. The three-dimensional organization of basicranio-facial architecture is controlled by the processes of flexure at the base of the skull, and this affects the morphogenesis of the two stages of the face, the maxilla and the mandible (Deshayes, 1986, 1988, 1991; Deshayes & Dambricourt Malassé, 1990; Dambricourt Malassé & Deshayes, 1992). This phenomenon, reviewed by Dambricourt-Malassé (1987, 1988, 1993, 2006), is found in all primates and in mammals generally. Cranio-facial contraction is minimal in prosimians, more substantial in monkeys (cercopithecids), even more so in great apes (*Pongo, Gorilla, Pan)* and australopithecines (*Australopithecus*), and maximal in humans. In all these species, qualitatively, the nature of the process is identical during embryogenesis, but, quantitatively, it is the embryonic amplitude of cranio-facial contraction that differs among the various present-day primates.

SHAPE CHANGES IN THE CRANIUM AND INCREASE IN CRANIAL CAPACITY

In recent papers (Chaline, 2003; Chaline et al., 1998; Millet, 1997; Penin, 1997), differences in the shape of the cranium in some species of great apes, australopithecines, fossil hominids, and modern humans have been quantified by geometric morphometry (David & Laurin, 1992; Felsenstein, 1990; Rohlf & Bookstein, 1990; Sneath, 1967). For eclampsia implications it is interesting to link increased cranial capacity in the *Homo* lineage with ontogeny. The cranio-facial contraction process starts very early in ontogeny, and during this period, neurons duplicate at the rate of 5000 neurons/second. But this process lasts 2 weeks after fertilization in chimpanzees, for example, while it continues for 8 weeks in humans. The extension of this period in humans thus brings about hypertrophy (fourfold) of the brain, and it is interesting to note that the end of this phase corresponds also with the second trophoblastic invasion. Cranial capacity ranges from 282 to 454 cm^3 in chimpanzees, from 350 to 752 cm^3 in gorillas, from 400 to 550 cm^3 in australopithecines, from 510 to 1600 cm^3 in archaic *Homo*, and from 1100 to more than 2000 cm^3 in *H. sapiens*.

According to this view of cranial capacity increase, it is clear that the very deep trophoblastic implantation occurring in humans as a two-phase process may be explained in terms of increased fetal nutritional needs compared with those in mammals with smaller cranial capacities. Thus, the appearance of preeclampsia in humans seems to be linked to the development of a large brain in *Homo*. The most archaic species of the human lineage (*habilis, ergaster, rudolfensis, erectus, heidelbergensis, neanderthalensis*) exhibit less cranio-facial contraction and smaller cranial capacity than *H. sapiens*. The large increase in cranial capacity observed in *H. sapiens* suggests that preeclampsia could be a byproduct of natural selection for that trait.

These considerations suggest a new hypothesis for the disappearance of *H. neanderthalensis* some 30,000 years ago (Chaline, 2003; Robillard, Chaline, et al., 2003). Within the archaic *Homo* bauplan, characterized by reduced cranio-facial contraction compared with *H. sapiens*, *H. neanderthalensis* exhibits the largest increase in cranial capacity of the group, reaching 1600 cm^3, a value that falls within the range of variability of *H. sapiens*. We may ask whether this large cranial capacity was compatible with fetal nutritional possibilities at such a primitive stage of cranio-facial contraction and ontogeny. A hypothetical but possible single-phase process of trophoblastic implantation may have been inadequate for this large increase in cranial capacity, occurring in an archaic structure, and this phenomenon may help to explain, at least partially, the disappearance of Neandertals. The two-phase process of very deep trophoblastic implantation in *H. sapiens* may have been an evolutionary solution, a new character, an innovation, or apomorphy allowing the extended fetal nutrition required by the large increase in cranial capacity.

POSSIBLE BIOLOGICAL CLUES FOR "EXTRAVAGANT" HUMAN SEXUALITY, LOW FERTILITY OF HUMAN FEMALES, AND "LOSS OF ESTRUS" IN HUMANS

Among mammals, the human species presents an apparent "extravagant" sexuality: most human copulations occur at the wrong time to result in fertilization. Copulation takes place throughout the cycle rather than in a period of estrus, and ovulation is concealed from male partner(s) and often even from females themselves (Diamond, 1992; 2000). Further, although extramarital sexuality is ubiquitous in human societies, the human female does not employ the reproductive strategy of her mammalian counterparts, placing the sperm of different males in competition at the time of ovulation. Marriage is an institution in almost all human societies, leading to a longer average fidelity in reproductive couples than in many other mammalian species (Diamond, 1992, 2000; Kaplan et al., 2000). At the same time, the human female displays a rather low rate of fecundity (25% per cycle at the age of maximum fecundity). It has been calculated that in order to conceive a human couple needs, on average (albeit there are numerous individual exceptions), about 100 acts of intercourse. Demographers calculate a mean time until conception in couples without contraception of 7–8 months after the beginning of sexual relations (Léridon, 1993). This is unusual compared with the situation of other mammals, whose sexual relationships during estrus are very fertile. Incidentally, it can be added that once having conceived, the human female has a somewhat high rate of spontaneous miscarriage (15%). At first glance, these facts could suggest that the human female is at some reproductive disadvantage compared to her nonhuman mammalian counterparts (Léridon, 1993). On the contrary, extensive exposure to the sperm of a particular male many times before conception (in fact, the life expectancy of sperm being 3 or 4 days in the female genital tract, even with intercourse twice a week, she is constantly exposed all the year long—a very rare situation among mammals) and many pregnancies with this same partner may be a biological adaptation to the risk of preeclampsia/eclampsia.

As noted, human females exhibit an unusually low fecundity rate when compared to other mammalian females. This seeming paradox is coupled with a risk of HDP as high as 40–45% in new couples with less than 4 months of cohabitation before conception. Low fecundity and risk of HDP with first pregnancy seems like an unusual reproductive strategy. Human females are exposed to a roughly 33% risk of HDP in first pregnancies in societies without modern contraception (Robillard, 1999, 2002). If, on the other hand, we experienced a fecundity rate of 75–90%, 50% of the first pregnancies (with roughly a 20% incidence of severe preeclampsia, and 5% of eclampsia) would experience HDP. Rather than being an advantage, becoming pregnant quickly after onset of sexual relations with a partner becomes a disadvantage with respect to preeclampsia risk. Thus, a fecundity rate of 25% seems to be the best compromise between preeclampsia in first pregnancies without threatening fertility for additional pregnancies (multiparity).

Loss of estrus in the human female remains partially unexplained (Pawlowski, 1999). Because of the apparent advantage of a low fecundability rate in humans due to the reduced risk of HDP, the protective effect of "sexual exposure" with a specific partner (lost with the absence of constant sexual cohabitation in primigravidae [Robillard, 1996]) favored human females who were sexually attractive and receptive across their entire cycle. The protective effect of keeping the antigens of a specific male partner for successive

births in women (lost in polyandry) induced a minimal rate of long fidelity in couples, probably not possible in estrus reproduction. The secondary and very deep specific trophoblastic implantation is coupled with the type of placentation, in which there is intimate exchange between maternal and fetal tissues (known as hemochorial placentation; see Figure 11-1). As a consequence, the successful pregnancy requires major maternal immunogenetic compromises in the face of foreign paternal antigens (Robillard et al., 2003a, b).

The cumulative net result arising from these various considerations would support the conclusion that the evolutionary strategy that occurred in humans seems to have been biased towards paternal tissue recognition through long sexual cohabitation in stable couples. Human reproductive characteristics that may also be related include loss of estrus, very low fertility rate, concealed ovulation, non-ovulatory sexuality, permanence of female sexual receptiveness and attractivity, absence of sperm competition in human females at the time of conception, and relatively large testicle size in human males (see Robillard et al., 2003a, b).

ETHNOLOGY: BIOLOGICAL, SOCIAL, AND CULTURAL ADAPTATIONS TO PREECLAMPSIA RISK

Infant as well as maternal mortality as a result of preeclampsia was a powerful selective force on the reproductive process of humans. The costs of preeclampsia are mitigated by exposure to the sperm of a particular male partner before a first pregnancy, providing females the opportunity to develop immunotolerance to foreign cells. This is coupled with a very low fertility rate and significant incidence of spontaneous miscarriage. In addition, there are cultural factors that serve to reduce mortality from HDP. For example, the majority of human cultures encourage marriages of long fidelity in reproductive couples (Diamond, 1992, 2000), and the vast majority of human groups prohibit polyandry (Deliège, 1996c). Further, the risk may have been an important contributing factor to the prohibition of incest in all human cultures (Robillard, Dekker, & Hulsey, 2002).

PREECLAMPSIA AS CONTRIBUTING FACTOR IN PROHIBITIONS OF INCEST AND SYSTEMATIC POLYANDRY

Except for some historical exceptions in royal families (ancient Egypt and Iran, Africa [Deliège, 1996a]), incest has been largely avoided in all human societies. Some anthropological literature states that incest avoidance is neither obligatory, nor properly human, nor a biological necessity, nor a social necessity. Arguments are that, except for genetic disorders, incest (i.e., parents/children, brothers/sisters) may have been a problem in only 1% of births. Even further, some scholars argue that appearance of homozygous deleterious genes by major incest would be advantageous as a means of getting rid of deleterious genes in the next generation (Langaney & Nadot, 1995).

In our view, avoidance of incest as a means to reduce preeclampsia risk may actually have a biological basis more significant than avoidance of the 1% risk of genetic disorders

(Robillard, Dekker, & Hulsey, 2002). Published reports suggest that fertility and pregnancy success is greater when parents are not genetically similar. It would appear that, biologically, females were favored to recognize the father's antigen as foreign (Grob, 1998). Couples with too similar tissue compatibilities often experienced repeated spontaneous abortions (RSAb), and the deleterious role of consanguinity has been extensively reported (Claman, 1993; Hussain, 1998; Surendeer, 1998; Zlotogora, 1997). Furthermore, after two, three, or four miscarriages during the first trimester, consanguineous couples—having finally achieved a "successful" pregnancy—experienced a significant increase of preeclampsia (Seidman, 1989; Thom, 1992). Contemporarily, this RSAb problem (i.e., at least three recurrent spontaneous abortions) occurs in very few couples (0.34%) by the random pairing of histocompatible partners in nonconsanguine populations (Claman, 1993). It would be expected to be much higher in societies where major incest was an accepted method of reproduction.

Concerning preeclampsia, recent data suggest that there is a highly significant increase of the female-to-male human leukocyte antigen (HLA) compatibility in couples experiencing preeclampsia (de Luca Brunori , 2000), but there are only a few epidemiological reports on preeclampsia risks among societies experiencing a high rate of reproduction between consanguines (cousins). Brocklehurst and Ross in 1960 (cited in MacGillivray, 1983) reported in Labrador 10 women with eclampsia in first pregnancy within an isolated group of British descent with considerable intermarriage across generations. Among them, five members of one generation from one family married five members of one generation from the same family. Of these five marriages, one remained sterile, and in the other four the women developed eclampsia. Three eclamptic women were married with cousins in the same family. There were eight cases of eclampsia over the three generations and three cases of eclampsia with the second pregnancy as well. The authors concluded that there was an inherited factor for eclampsia transmitted through the female line. Conversely, Stevenson et al., in 1976 (cited in MacGillivray, 1983), described a case-control approach to a population in Ankara where consanguineous marriages were frequent. Consanguinity was less frequent in women with preeclampsia (they did not present their results of women by primigravidity and other parities and consanguinity).

It is of note that among 565 cultures described (Deliège, 1996b), only two polyandric cultures have been reported: the Toda in southern India and the Nyinba people in Nepal (Deliège, 1996c). Interestingly, in these two groups, polyandrous unions occurred obligatorily, with brothers of the same family (adelphic polyandry) marrying the same wife. Conversely, inside the small high caste of Nayars in Kerala, South India, reproductive unions occurred with apparently total free polyandry. In addition to explanations of low polyandry as a means of ensuring male parental care or patriarchal control of women's fertility, an absolutely free systematic polyandry might have been noticed to contribute to higher preeclampsia/eclampsia risk and thus lower fertility.

ETHNOLOGICAL ASPECTS

Because of the importance of eclampsia in humans, ethnographers should be able to collect information on different human interpretations concerning convulsions and pregnancy.

The association between delivery and seizures should be recorded in one way or another in human memories (e.g., in myths, tales, songs). Cultural development of morals of these stories should be very instructive with regard to their interpretations of convulsions in childbirth. Particularly, it would be interesting to investigate whether this "curse" is directed toward the mother only or toward the couple. If the latter is the case, it may be that past cultures had noticed facts that modern medicine has taken a long time to rediscover.

CONCLUSION

HDP, and especially preeclampsia, are frequent in both the developing and developed world. In developed areas, hypertension is often associated with kidney or liver injury, and hospitalization is usually recommended. In case of threatening signs of eclampsia (maternal convulsions), the only treatment is to perform an emergency cesarean section and deliver the fetus and the placenta. This is a frequent concern of obstetricians and neonatologists and has implications for epidemiologists, biologists, immunologists, demographers, anthropologists, palaeoanthropologists, ethnologists, geneticists, zoologists, and others. Many of these disciplines have not been traditionally included in discussions of HDP.

The authors of this chapter are not aware of any ethnographic report of eclampsia or its associated convulsions and high mortality, notwithstanding that this is a common human reproductive complication factor with both biological and cultural implications. We encourage ethnographers to engage women, sorcerers, shamans, and other healers with the simple question: "What is the meaning of a young woman dying with convulsions giving birth?" Responses should give some clues of the extent to which this problem is known across cultures.

Further research to describe the biological pathways explaining the global reversible endothelial inflammation that is encountered in women presenting preeclampsia/eclampsia (Roberts et al., 1989) and the mechanisms of the paternal–maternal immunological conflicts leading to the poor implantation of certain human trophoblasts (Chaouat et al., 2005, Dekker & Robillard, 2005) is required. At the beginning of this twenty-first century, there are some hopes that these biological clues can be finally fully understood within one or two decades.

For zoologists, anthropologists, and others working in comparative reproduction, knowledge of hypertensive disorders of pregnancy may give clues to understanding certain features of human reproduction, including the two-wave implantation of the human trophoblast, the very low fertility rate of human females, loss of estrus, concealed ovulation, "continuous" sexuality, absence of sperm competition in human females at the time of ovulation, relatively large testicle size in human males, prohibition of incest, and low frequency of systematic polyandry in human cultures (Robillard et al., 2002, 2003a, b). If it is true that the "two-wave" process of implantation of the trophoblast is unique to humans, palaeoanthropologists may hypothesize that the appearance of preeclampsia during hominization may have arisen at a point in human evolution that brain mass of *Homo* fetuses increased to a critical point. Perhaps HDP can even help to explain the disappearance of the Neanderthals (Chaline, 2003).