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An Evolutionary Approach to Human Premature Labour

Ray Carson and David Miles

Perinatal and Maternal Studies Research Group, Division of Biomedical Sciences, School of Health Sciences, University of Wolverhampton, Wolverhampton, UK

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Abstract: Premature labour in humans is a major obstetric complication affecting up to 10% of births. Humans appear to be more predisposed to premature labour compared to other eutherian mammals. The aim of this paper is to attempt to use an evolutionary and comparative approach to consider the reasons for human predisposition to premature labour. There appear to be evolutionary trends in the mechanism of the initiation of labour, which could make some species more susceptible to premature labour. The main causes of human premature labour appear to be intrauterine infection and incompetence of the cervix, although fetal and maternal stress could also be involved. Possible reasons for human predisposition to premature labour may include susceptibility to intrauterine infection, the critical role of the cervix, the short breeding cycle, the type of placentation and the relative size of the fetal head. A relatively high incidence of preterm delivery does not affect overall human reproductive success. By using a comparative and evolutionary approach to human premature labour it is possible to gain a broader understanding of this problem within its biological context.

Resumo: *Uma abordagem evolucionária para explicar o parto prematuro humano.* O parto prematuro humano é uma grande complicação que afeta 10% de todos os nascimentos. O ser humano parece estar mais prediposto ao parto prematuro do que outros mamíferos etéreos. O objetivo deste artigo é explicar, através de uma abordagem evolucionária e comparativa, as razões para tal predisposição. Parece que existem tendências evolucionárias no mecanismo de iniciação do parto, tornando algumas espécies mais susceptíveis ao parto prematuro. As causas principais do parto prematuro são infecção intrauterina e incompetência do cervix, apesar de que o estresse matemo e fetal podem também estar envolvidos. A predisposição humana para o parto prematuro pode ser explicada pela susceptibilidade para infecção intrauterina, o papel crítico do cervix, o período curto de gestação, o tipo de placentação e o tamanho relativamente pequeno da cabeça do feto. A incidência relativamente alta de parto prematuro não afeta o sucesso geral do ser humano. Usando uma abordagem comparativa e evolucionária para explicar o parto prematuro, é possível adquirir uma compreensão mais geral do problema dentro do contexto biológico.

Correspondence to: Dr. Ray J. Carson, School of Health Sciences, University of Wolverhampton, Wolverhampton WV1 1DJ, UK, Telephone 01902 321141, Telefax 01902 321161, e-mail R.J.Carson@wlv.ac.uk

Introduction

Preterm birth can be defined as occurring before 90% of the normal gestation period. Human premature labour can be defined as uterine contractions with sufficient intensity, duration and frequency to produce progressive cervical effacement and dilatation before 37 weeks of gestation. Preterm birth is a major obstetric problem, affecting up to 10% of births in the UK and USA (Keirse 1995). In the UK around 40,000 babies are born prematurely each year, and this accounts for 60% of all neonatal deaths (Costeloe 1998). A recent survey in the UK found extensive neonatal mortality among premature infants (Magowen et al. 1998). Those premature babies that survive may have long-term sequelae, and the social and financial cost of care is high. The picture is similar in the U.S.A. where 11% of infants are born prematurely, and prematurity accounts for 58.6% of all infant deaths (Keirse 1995). Premature labour is clearly a major public health problem.

Aetiology of Human Premature Labour

Although the exact mechanisms involved in the initiation of premature labour in women are unknown, some risk factors have been identified, which are summarised in Table 1 (Carson 1997a). Of these, intrauterine infection seems to be the main cause. Intrauterine infection is a known risk factor for preterm labour and is associated with the pathology of the condition (McGregor et al. 1988; Romero and Mazor 1988; Toth et al. 1988). There is evidence of an association between intra-amniotic infections and preterm labour and delivery (Yen 1991; Radetsky 1994; Romero and Mazor 1988). The positive link between bacterial vaginosis and preterm birth has been recently reviewed (Chaim et al. 1997; Paige et al. 1998). A meta-analysis of studies has also identified a positive association between urinary tract infection during pregnancy and an increased risk of preterm delivery (Romero et al. 1989).

Table 1. Possible risk factors for premature labour in humans.

• Infection of the uterus, cervix or urinary tract
• Uterine abnormality or incompetent cervix
• Maternal disease: diabetes, hypertension, hyperthyroidism
• Multiple gestation or fetal abnormality
• Placenta previa or abruption
• Premature rupture of the membranes
• Low socio-economic group of the mother

There is increasing evidence that an inflammatory process is involved in the initiation of normal parturition at term (Kelly 1996) and this could also be involved in preterm delivery. In intrauterine infection, bacteria enter the uterus via the vaginal route and, in so doing, would have to penetrate the mucus plug which usually blocks the cervical os during pregnancy. The bacteria are thought to rupture the amniotic sac by releasing protease and phospholipase enzymes. Once in the amniotic fluid the bacteria stimulate macrophages and set off a cascade of events (Fig. 1). The activated macrophages release inflammatory mediators

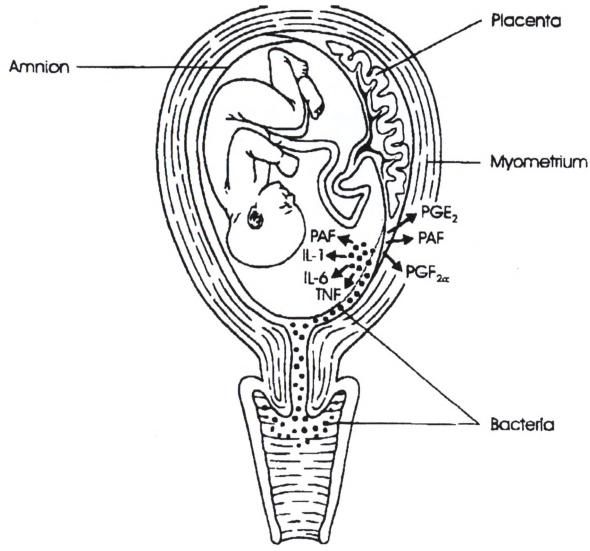

Fig. 1. A model of intrauterine infection and subsequent inflammation as a possible mechanism involved in human premature labour.

such as interleukin-1 (IL-1), tumour necrosis factor alpha (TNFα), interleukin-6 (IL-6), and platelet activating factor (PAF) (Yen 1991; Radetsky 1994; Romero and Mazor 1988). These mediators are all thought to play a role in the initiation of normal term labour. Intact fetal membranes have been shown to produce inflammatory mediators, such as prostaglandin E_2 and $F_{2\alpha}$ (Rajasingam et al. 1998), IL-6 and IL-8 (Fortunato et al. 1998), and nitric oxide (Seyffarth et al. 1999) in response to bacteria and bacterial products, such as lipopolysaccharide (LPS). These inflammatory mediators diffuse locally and stimulate the production of prostaglandin E_2 and $F_{2\alpha}$, which are known to cause myometrial contraction and to have a key role in initiating parturition. If sufficient quantities of prostaglandins E_2 and $F_{2\alpha}$ are produced in the region of the myometrium, then regular contractions occur and the process of labour is initiated. So there appears to be a mechanism by which intrauterine infection can cause the release of inflammatory mediators, which initiate myometrial contractions leading to premature labour. However, there is an alternative view that intra-uterine infection is not a cause of premature labour, but an effect of it (Radetsky 1994). This theory suggests that dilation of the cervix in premature labour allows greater access of bacteria to the uterus. The consensus view at the moment appears to be that intra-uterine infection is a possible cause of premature labour.

The role of the cervix in human pregnancy seems to be very important. A failure of the cervix to retain the conceptus can trigger premature labour. Women with a shorter cervix have been found to have twice the risk of premature labour. The length of the cervix, as measured by ultrasound scan, has been found to correlate with the length of gestation (Lockwood 1995). In some women, the cervix is not fully competent and does not remain closed as the fetus grows, again increasing the risk of preterm delivery.

Maternal health is linked to premature labour and some diseases are thought to be risk factors (Table 1). In wild populations of animals, diseased individuals would probably not survive to breed, although infection could occur during pregnancy, which might induce premature labour. In human society the situation is rather artificial and maternal disease is relatively prevalent and is a risk factor for premature labour.

Fetal abnormality could be a stimulus for preterm delivery, but it is more likely to occur in early pregnancy. In theory, miscarriages should occur as early as possible during pregnancy, in order to minimise the cost to the mother. It has been estimated that most conceptions miscarry before the 12th week of pregnancy (Edmonds et al. 1982) and that 78% of human conceptions never reach term (Roberts and Lowe 1975).

Fetal distress in utero has been suggested as a cause of premature labour. Work in sheep has shown that the hypothalamic-pituitary-adrenal (HPA) axis is centrally involved in the initiation of labour at term. The hormones corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol have been shown to be involved. Increasing concentration of cortisol in the fetal lamb's blood stimulates the production of 17β-oestradiol by the placenta. Increasing concentration of 17β-oestradiol stimulates the local production of prostaglandins E_2 and $F_{2\alpha}$ leading to the initiation of parturition. In theory, fetal stress in utero could initiate premature labour in sheep by increasing the release of cortisol. However, in humans this mechanism cannot occur because the placenta lacks the crucial enzyme, 17α-hydroxylase, which converts progesterone to 17β-oestradiol. In terms of evolutionary trends, it seems that in humans the placenta has taken over the dominant role of the fetal HPA axis evident in sheep. This area of research is controversial, as some workers do claim that CRH and ACTH are involved in the initiation of human parturition (McLean et al. 1995). It is possible that fetal stress in utero could trigger premature labour in women, but the mechanism has not yet been elucidated. There is no definitive evidence that fetal stress arising from malnutrition or placental insufficiency are direct causes of preterm delivery in humans.

Maternal stress could be a causative factor in premature labour. Activation of the HPA axis would increase the circulating levels of CRH, ACTH and cortisol, which some workers believe are involved in the initiation of human labour. Anecdotal evidence suggests that severe maternal stress can induce premature labour. Cortisol is able to cross the placenta and enter the fetal circulation. This is known to affect the HPA axis in the fetus (Weinstock 1997), but it is not clear whether this could trigger premature labour. Certainly in other mammals maternal stress causes loss of fetuses. In some mammals, maternal stress at a critical time during pregnancy causes resorption of the fetuses, but this mechanism is clearly absent in humans. Many mammals, such as gorillas, baboons and lions, live in hierarchical social groups, which experience occasional changes in the dominant male. Such conditions are probably stressful for pregnant females and may disfavour carrying a fetus fathered by a previous dominant male. This might select for a mechanism for losing the fetus prematurely and returning to breeding capability. Presumably, sacrificing the fetuses increases the chances of the mother being able to survive and breed again. This mechanism has probably been selected for in response to

predation or the social environment, however this selection pressure should not be effective in human society. Wasser (1999) has recently published an interesting review that takes an evolutionary approach to stress and reproductive failure.

From an epidemiological point of view the incidence of premature birth is higher in lower socio-economic groups, suggesting a link with poverty (McLean et al. 1993). This is probably multifactorial and could include maternal diet, stress, health and access to medical care. From a social point of view, alleviating the worst effects of poverty would reduce the incidence of premature birth. An economic aid and educational scheme in France did indeed reduce the incidence of preterm birth (McLean et al. 1993).

Incidence of Preterm Delivery in Other Mammals

It is difficult to obtain epidemiological data on the incidence of spontaneous preterm delivery in wild and domesticated animals. The incidence of spontaneous premature parturition is relatively low in most domestic species, which usually deliver within a fixed period (Silver 1992). The horse is an exception, as it has a wide range in gestational length (320–360 days) and a higher incidence of spontaneous preterm delivery (Rossdale and Silver 1982). One possible factor involved is sensitivity of the myometrium to oxytocin, as smooth muscle cells of the myometrium in the horse express oxytocin receptors from 300 days gestation (Silver 1992). Poor maternal nutrition in late pregnancy is definitely linked to premature labour in domesticated animals (Fowden and Silver 1983; Stammers et al. 1988). Placenta previa has been reported in cattle, but it was associated with perinatal mortality and not preterm delivery (Mee 1991).

In a colony of captive chimpanzees the incidence of spontaneous pregnancy termination was found to be relatively low (Meiss et al. 1990), although preterm delivery of chimpanzee infants has been reported in the literature (Alford et al. 1991). In a large study of rabbit fertility under laboratory conditions, a low incidence of premature delivery was reported (1.6% in a total population of 1,795) (Feussner et al. 1992). However, it has been found that stress induced by overcrowding can cause premature labour in rabbits (Mykytowycz and Fullagar 1973). An unusually high reported incidence (20%) of premature parturition in a wild population of Californian sea lions was thought to be due to a combination of disease agents and environmental contaminants (Gilmartin et al. 1976). Dolphins have a high brain size to body size ratio and a relatively long gestation period (12 months), however incidences of preterm birth are not well documented. It is possible that the aquatic environment is protective against vaginal infection and that the effect of the weight of the fetus on the cervix is removed by the buoyancy of the water.

Human Predisposition to Preterm Delivery

It is not clear why humans appear to be particularly susceptible to premature delivery, compared to other eutherian mammals. There are species differences in the physiological mechanisms involved in the maintenance of pregnancy, and in the initiation of labour, between mammalian groups. A recent theory has suggested that far from pregnancy being a symbiotic relationship, the fetus behaves,

in biological terms, more like an aggressive parasite (Haig 1993). The demand of the fetus for nutrients can even endanger the life of the mother, for example in pre-eclampsia. Pregnancy appears to be a delicate balance between the invasion of the trophoblast into the maternal endometrium and the mother's immune response to this genetically distinct tissue. The maternal-fetal relationship has been shaped by natural selection, as stated by Haig (1993). A recent hypothesis has suggested that the maternal systemic innate immune system is activated during pregnancy (Sacks et al. 1999). This contradicts previous theories, which proposed a state of immunosuppression during pregnancy (Medawar 1953). It is not then surprising that sometimes this delicate balance is upset and premature labour is initiated.

In light of the "Selfish Gene" theory (Dawkins 1989), it can be understood why the survival of the fetus is paramount, to pass on its genes, at the expense of the survival of the mother. However, with the uniquely long period of parental care in humans it does not appear to be in the fetal interest to be responsible for the death of the mother. In early human society, orphaned infants may have been cared for within a social group. As women are not tied to a fixed breeding season, but are fertile at roughly monthly intervals, a fetus which is lost by preterm delivery could be replaced fairly rapidly. While it is difficult to make comparisons, humans also appear to be distinct in the strong bonding between parents and infant. Every loss due to preterm delivery is a personal tragedy. However, in terms of passing on genes, it would be more effective for a mother to abort a fetus if any problems in the pregnancy occur, to enable her to become pregnant again as soon as possible. Although premature labour might seem disadvantageous, in evolutionary terms it has not been removed by selection pressure, in fact it is quite prevalent, suggesting that it must convey some advantage. Perhaps the high incidence of preterm delivery in humans is evidence of an evolutionary trend toward a shortening of the gestation period, although the advantage of this is not obvious. As the mother usually survives premature labour, selection pressure may not operate directly, but reproductive success could be compromised. The usual singleton fetus in human pregnancy represents a high investment in the survival of the fetus to term and beyond, compared to multiparous mammals.

The exact mechanism of initiation of parturition in humans is not known (Carson 1997b). It is logical to assume that the fetus is able to signal to the mother when it is sufficiently mature to survive outside the uterus. If conditions become threatening in utero, and the fetus initiates labour, then there must be an assessment of the risk to survival of remaining in utero or moving ex-utero. As the incidence of premature labour is relatively high, this suggests that the risk/benefit ratio favours the strategy of triggering labour and undergoing preterm delivery, in the hope of fetal survival.

Uniquely in humans the cervix has to retain the conceptus in utero against the force of gravity, due to our upright posture. The role of the cervix in human pregnancy is paramount and appears to be much more important than in other mammals. However, some mammals, such as monkeys and apes, do adopt an erect posture, so the role of the cervix might be equally as important as in humans. It is not known why these groups are less prone to premature labour compared to humans. If intrauterine bacterial infection, via the cervix, is a major cause of pre-

mature labour, then it is not clear why humans appear to be more susceptible to this. Most mammals have a fixed breeding season, outside of which sexual activity does not occur, whereas humans seem to be distinct in continuing sexual activity even throughout pregnancy. However, studies in humans have found no link between coitus during pregnancy and bacterial vaginosis, premature rupture of the membranes or preterm birth (Ekwo et al. 1993; Kurki and Ylikorkala 1993).

There are differences between mammals in the morphology of the placenta and the type of placentation. Epitheliochorial placentas occur in pigs, horses, whales and lemurs, and involve little or no invasion of maternal tissue (Haig 1993). Conversely, haemochorial placentas involve extensive invasion of the endometrium, and occur in humans as well as monkeys, apes, rodents, rabbits and bats (Haig 1993). In such placentas the maternal and fetal blood are separated by a thin layer of syncytiotrophoblast and the anatomical relationship between the two bloods is intimate. Therefore the fetus has better access to the maternal blood circulation for signalling purposes. Perhaps the invasive nature of the haemochorial placenta, in order to gain a better nutrient supply for the fetus and to improve fetal/maternal signalling, carries an increased risk of premature labour, in species such as humans.

In humans, the fetal head is relatively large to allow for development of an increased brain capacity. The ratios of fetal head circumference to the size of the cervix, the pelvis and the diameter of the birth canal are all relatively high, compared to other mammals. Parturition in humans carries considerable risk to the fetus and the mother. The timing of parturition has presumably evolved to allow the fetus maximum benefit from intrauterine nutrition, while minimising the increasing risks of delivery (Haig 1993). This suggests that the maternal genes would favour a shorter gestation period, to minimise the risks of delivery, at the expense of fetal growth. Thus the mother should be responsible for initiating premature delivery, however this clearly contradicts the current view that the fetus is responsible for triggering labour. Humans are distinct in having a relatively long gestation period for their body size, compared to other mammals (Table 2). Perhaps the cost of a long gestation is an increased risk of preterm delivery, however this is not evident in dolphins, for example. *Homo sapiens* evolved relatively rapidly as a species and it is possible that some of the advantages gained, such as increased intelligence, had a biological cost in terms of an increased predisposition to preterm delivery.

Conclusion

Premature labour is still a major medical problem. Humans appear to be more predisposed to premature labour compared to other mammals, although the reasons for this are not yet clear. Possible reasons include susceptibility to intrauterine infection, the critical role of the cervix, the short breeding cycle, the type of placentation and the relative size of the fetal head. In view of the reproductive success of humans as a species, premature labour does not appear to be disadvantageous, but may even convey an overall advantage. While using a comparative and evolutionary approach is useful for gaining a broader understanding of human premature labour within its biological context, it does not provide any concrete answers. Per-

Table 2. A comparison of the gestation period, incidence and known risk factors associated with preterm delivery in some eutherian mammalian species.

Species	Gestation period (days) mean	Gestation period (days) range	Incidence of preterm delivery	Risk factors
Human	280	252–294	up to 10%	intrauterine infection (see Table 1)
Sheep	148	144–153	very low	maternal under-nutrition
Horse	340	320–360	high	maternal under-nutrition
Rabbit	31	30–32	low	maternal stress
Dolphin	365		low ?	not known
Chimpanzee	230		low	not known
Cow	282	275–290	low	not known
Sea lion	350		high	disease and toxins

haps an increased risk of premature labour is a result of the evolutionary path of humans, such that we are victims of our own rapid evolution. There is clearly a need for more research in the area of human premature labour.

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