Cliff-edge model predicts intergenerational predisposition to dystocia and Caesarean delivery

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Recently, we presented the cliff-edge model to explain the evolutionary persistence of relatively high incidences of fetopelvic disproportion (FPD) in human childbirth. According to this model, the regular application of Caesarean sections since the mid-20th century has triggered an evolutionary increase of fetal size relative to the dimensions of the maternal birth canal, which, in turn, has inflated incidences of FPD. While this prediction is difficult to test in epidemiological data on Caesarean sections, the model also implies that women born by Caesarean because of FPD are more likely to develop FPD in their own childbirth compared with women born vaginally. Multigenerational epidemiological studies indeed evidence such an intergenerational predisposition to surgical delivery. When confined to anatomical indications, these studies report risks for Caesarean up to twice as high for women born by Caesarean compared with women born vaginally. These findings provide independent support for our model, which we show here predicts that the risk of FPD for mothers born by Caesarean because of FPD is 2.8 times the risk for mothers born vaginally. The congruence between these data and our prediction lends support to the cliff-edge model of obstetric selection and its underlying assumptions, despite the genetic and anatomical idealizations involved.

Caesarean section | human evolution | obstetrical dilemma | obstructed labor | quantitative genetics

Recently, we presented a mathematical model—the cliff-edge model (1)—to explain the evolutionary persistence of the relatively high incidences of cephalopelvic disproportion and shoulder dystocia in human childbirth. We use the term fetopelvic disproportion (FPD) to refer to both of these origins of disproportion between fetal and maternal dimensions, with reported incidences ranging from about 1 to 8% (2–4). In industrialized countries, FPD usually leads to delivery by Caesarean section (C-section) to prevent maternal and neonatal morbidity or mortality.

The cliff-edge model is based on an idealized variable, D, that represents the difference between the size of the neonate and that of the maternal birth canal. Medical data document higher survival rates for larger neonates (5, 6) and lower rates of pelvic floor disorders in women with narrower pelvises (7, 8), and thus an increase in reproductive success (i.e., evolutionary fitness) with D. This directional selection toward larger D is counterbalanced by obstetric selection: If neonatal size exceeds the size of the birth canal ($D > 0$), fitness drops sharply in the absence of medical care (9–13). For an approximately symmetrically distributed phenotype D, the balance between these selective forces at the evolutionary stable state entails a constant rate of FPD (Fig. 1 *A* and *B*).

With the safe availability of C-sections, obstetric selection has diminished in most industrialized countries. As a result, the size of the fetus relative to that of the birth canal is expected to increase due to the remaining directional selection (Fig. 1*C*). All other factors assumed constant, the cliff-edge model predicts that, since the wide application of C-sections in the mid-20th century, D has increased evolutionarily by about 0.04 to 0.08 standard deviations, inflating the initial FPD rate by 10 to 20%, which is roughly half a percentage point (1, 14).

Our prediction, which has provoked wide response in the scientific community and the public, is difficult to prove empirically, because FPD is difficult to diagnose directly and the evolutionary increase of D may be concealed by countervailing factors such as reduced gestational age (14). C-section rates—as indirect measures—have increased, for a number of reasons other than selection, from a few percent up to 20% or 30% in most countries and vary significantly between countries, hospitals, sociocultural groups, and age cohorts [e.g., refs. 15 and 16]. However, the cliff-edge model also implies that women who were born by C-section because of FPD are more like to develop FPD and to deliver by Caesarean in their own childbirth, compared with women who were born vaginally.

Multigenerational Model of FPD

In the cliff-edge model, the fraction of women who develop FPD during childbirth (that is, with $D > 0$) is given by the area under the probability density function beyond the cliff edge (the red area in Fig. 1*B*), whereas women with $D \leq 0$ have a birth canal that can accommodate the fetus. Let us assume that both groups of women mate randomly (with respect to D) with a male from the full population and that maternal and paternal allele effects recombine additively. Assume further an initial FPD rate of 2%, which is in the lower range of reported data, and a heritability of 0.5 for D based on studies of newborn intracranial volume and maternal pelvic dimensions (1, 17–20). Then the model predicts that women who were born by Caesarean because of FPD are 2.8 times more likely to develop FPD in their own childbirth compared with women born vaginally (this equals a relative risk or "risk ratio" of 2.8; see *Methods* and Fig. 2 for computational details).

Significance

The cliff-edge model explains the evolutionary persistence of relatively high incidences of fetopelvic disproportion (FPD), the mismatch of fetal and maternal dimensions during human childbirth. It also predicts that FPD rates have increased evolutionarily since the regular use of Caesarean sections. Here we show that the model also explains why women born by Caesarean because of FPD are about twice as likely to develop FPD in their own childbirth compared with women born vaginally. This theoretical prediction of a complex epidemiological pattern lends support to the cliff-edge model and its underlying assumptions.

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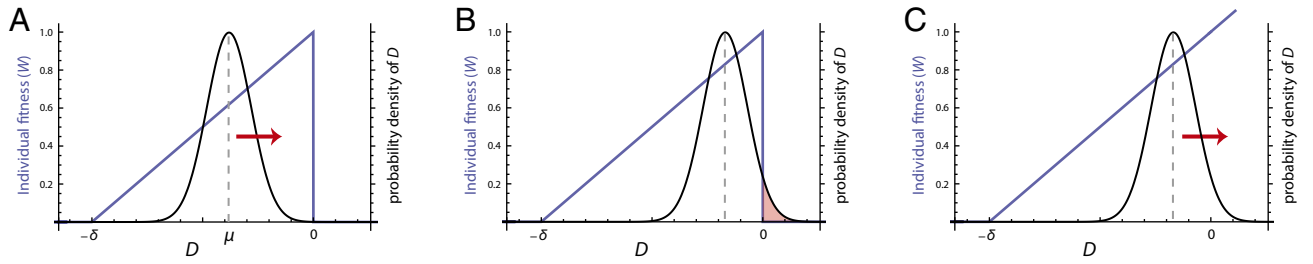

Fig. 1. The cliff-edge model of obstetric selection. (*A*) The difference, *D*, between neonatal size and maternal pelvic canal size is approximately normally distributed in a population (black curve) with mean μ (dashed line) and unit variance, which is assumed to stay constant. Individual female fitness (blue curve) increases linearly with *D* to its maximum at $D = 0$; thereafter, fitness drops sharply (without C-section) because of FPD. This directional selection induces an evolutionary increase of *D*. (*B*) In evolutionary theory, natural selection maximizes average population fitness (average number of offspring per individual). Because of the asymmetric "cliff-edged" fitness function, the trait mean that maximizes population fitness always entails a fraction of individuals with FPD, i.e., with $D > 0$ (the red area). This fraction does not depend on the scale and sexual dimorphism of *D*, but increases with the genetic correlation between the sexes (for more details, see ref. 1). (*C*) C-sections remove the fitness threshold at $D = 0$, thus leading to a further evolutionary increase of *D* and the resulting FPD rate.

This risk ratio well above 2 should be easily detectable in multigenerational epidemiological data. Note that this prediction refers to Caesareans caused by FPD only, not to elective Caesareans or to those carried out for other reasons. However, owing to the difficulty of diagnosing FPD, most epidemiological data are either about C-section rates or, more generally, about obstructed labor or dystocia. Because surgical delivery and dystocia can result from numerous other reasons than FPD—including psychological, social, and other biological factors (21–23)—the risk ratio for Caesarean/dystocia between women delivered by Caesarean/dystocia and those who were not is expected to lie below our prediction.

Multigenerational Epidemiology of C-Section

Algovik et al. (24) studied the incidence of dystocia (obstructed or delayed labor) in more than 2.5 million individuals from the Swedish Birth, Twin, and National Family Registers. They reported that mothers who were born with dystocia had 1.66 times the risk of developing dystocia in their own labor compared with a mother born without dystocia. The authors identified a negligible influence of the shared environment between relatives but a strong effect of the nonshared environment. Similarly, in 48,000 Swedish mother–child pairs, Berg-Lekås et al. (25) found that, if a mother had dystocia (resulting in instrumental intervention) when delivering her eldest daughter, this daughter faced a risk ratio of 1.8 for developing dystocia during her own first childbirth. Both studies, however, did not differentiate between the different reasons for obstructed labor.

Tollånes et al. (26) studied C-sections in more than 440,000 Norwegian grandmother–parent units. A mother born by Caesarean had 1.55 times the risk of having her first child by Caesarean compared with a mother born vaginally. This association was not found for fathers born by C-section; their partners showed no increased risk of having their first child by Caesarean. When confining the analysis to a low-risk subgroup that excluded women with "a record of pre-eclampsia, pregestational diabetes, breech delivery, abruptio placentae, placenta previa or dystocia," as well as units with birth weights below 2,500 g or above 4,500 g or a gestational age below 37 wk or above 42 wk, this risk ratio even increased to 2.06. The presence of detectable association in grandmother–mother units but not in grandmother–father units indicates that "social inheritance" of C-section is weak, at least via the father.

In a study of operative delivery in more than half a million cases from Utah, Varner et al. (2) distinguished cephalopelvic disproportion from dysfunctional and prolonged labor. Pooled over all these indications, a woman who was herself delivered by Caesarean had 1.41 times the risk of delivering by Caesarean compared with a woman born vaginally. The subgroup delivered by Caesarean because of cephalopelvic disproportion (limited to pregnancies with vertex presentation) faced a risk ratio of 1.83 of delivering their own children by Caesarean.

Conclusions

The evolutionary increase of FPD rates as predicted by the cliff-edge model is difficult to observe in epidemiological data on

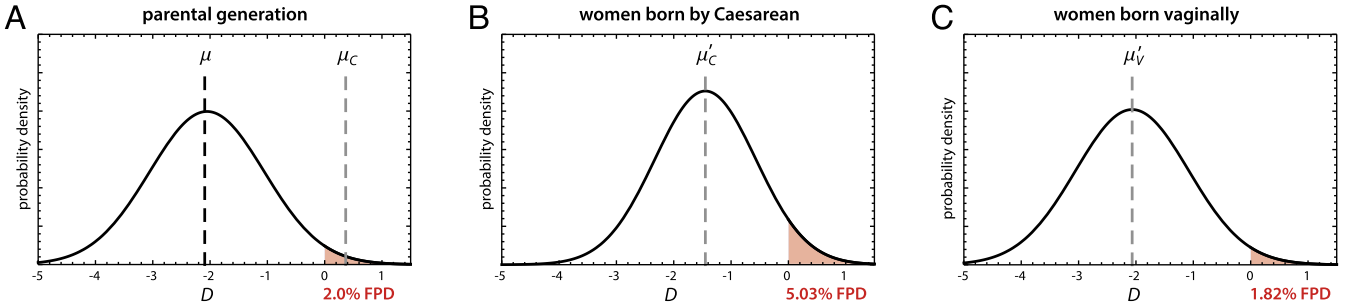

Fig. 2. Multigenerational model of FPD. (*A*) The black curve represents the normal distribution of *D*, with mean $\mu = -2.05$ (black dashed line) and unit SD, entailing an FPD rate of 2% (the fraction of individuals with $D > 0$, represented by the red shaded area). These mothers delivering by Caesarean because of FPD ($D > 0$) have a mean of $\mu_C = 0.37$ (gray dashed line) and an SD of $\sigma_C = 0.33$. (*B*) These mothers mate with a male from the full distribution centered at $\mu = -2.05$, and thus their offspring—the generation born through Caesarean—has intermediate trait mean $\mu'_C = -1.45$ and SD $\sigma'_C = 0.88$, resulting in an FPD rate of 5.03% (the red area). (*C*) Women born vaginally, by contrast, have a mother with $D \leq 0$ and a father from the original distribution, leading to a mean $\mu'_V = -2.07$ and variance $\sigma'_V = 0.99$ with a 1.82% FPD rate (red area). Hence, mothers born by Caesarean because of FPD have a $5.03/1.82 = 2.77$ times higher risk of developing FPD in their own childbirth than mothers born vaginally.

operative delivery. However, the model also implies that women who were born by Caesarean because of FPD face an increased risk of developing FPD in their own childbirth. Based on the above-mentioned assumptions, the model predicts a risk ratio of 2.8, an effect size much larger than that of the predicted evolutionary change.

Large-scale epidemiological studies indeed evidence that women born by C-section are more likely to deliver by Caesarean than women born vaginally, owing primarily to genetic rather than social factors. When pooling over all of the different causes for Caesarean and dystocia, the reported risk ratios range from 1.4 to 1.8. These estimates are below our prediction of 2.8, which specifically refers to Caesareans caused by the disproportion of anatomical dimensions. Social and other nonanatomical reasons for Caesarean delivery, including presentation of the fetus, that show little or no heritability deflate these empirical estimates of intergenerational predisposition. After excluding many nonanatomical factors of dystocia in Tollånes et al. (26), and also in Varner et al. (2), who calculated risks specifically for cephalopelvic disproportion, the reported risk ratios were close to 2. This is closer to our prediction but still underestimated due to the difficulties in diagnosing FPD.

In summary, these estimated risk ratios fit well to the prediction of the cliff-edge model: They are below the prediction but in the same order of magnitude. This congruence of empirical data and the prediction lends support to the cliff-edge model of obstetric selection and its underlying assumptions, despite the genetic and anatomical idealizations involved.

Methods

Let the difference, D, between fetal size and pelvic canal size be normally distributed with unit SD (the latter choice does not restrict generality): $P(D) = P(D, \mu, \sigma) \sim N(\mu, 1)$. FPD occurs iff $D > 0$; hence an FPD rate of $r = 2\%$ implies a mean of $\mu = -2.05$ (Fig. 2*A*),

$$r = \int_0^\infty P(D, -2.05, 1)dD = 0.02.$$

Based on this simple model, we want to estimate the FPD rate in the offspring of these 2% of women who delivered by Caesarean due to FPD, and compare it to the FPD rate in the offspring of the 98% of women who delivered vaginally. We thereby assume that women from both groups mate randomly with respect to D with a male from the full distribution $P(D, -2.05, 1)$. Furthermore, we assume additivity of maternal and paternal alleles with no genotype-by-environment interaction and parent-of-origin effect.

The mothers with $D > 0$ who delivered by C-section have the mean

$$\mu_C = \frac{1}{r}\int_0^\infty P(D, -2.05, 1)D\,dD = 0.37 \quad [1]$$

and SD

$$\sigma_C = \left(\frac{1}{r}\int_0^\infty P(D, -2.05, 1)(D-\mu_C)^2 dD\right)^{-1} = 0.33. \quad [2]$$

The mean phenotypic difference between these parents and their offspring can be expressed via the breeder's equation, that is, as the product of the "selection differential" and the heritability (27). In standard quantitative genetic contexts, the selection differential is the difference between the average phenotypes before and after selection in one generation. In our case, the average phenotype before selection is $\mu = -2.05$, while the average phenotype after selection is $\frac{1}{2}(\mu_C + \mu)$ because half of the individuals (the mothers) are from the "selected" distribution with $\mu_C = 0.37$ and the other half (the fathers) are from the full distribution centered at $\mu = -2.05$. The selection differential thus is $\frac{1}{2}(\mu_C + \mu) - \mu = \frac{1}{2}(\mu_C - \mu)$. In Mitteroecker et al. (1), we assumed a heritability of $h^2 = 0.5$ for D, based on studies of newborn intracranial volume and pelvic dimensions. Thus, the mean offspring phenotype of the mothers delivering by Caesarean equals

$$\mu_C' = \mu + \frac{1}{2}(\mu_C - \mu)h^2 = -1.45. \quad [3]$$

These mothers who delivered by Caesarean represent just a small part of the population with reduced genetic variance, whereas their mates—the fathers—are chosen from the full distribution with unit variance. Under the assumptions listed above, the phenotypic variance, σ^2, can be expressed as the sum of the variances of maternal and paternal allele effects plus the environmental variance: $\sigma^2 = \sigma_P^2 + \sigma_M^2 + \sigma_e^2$, which totals 1 for the original distribution of D. It follows that the genetic variance resulting from one allele is given by

$$\sigma_P^2 = \sigma_M^2 = \frac{1}{2}h^2\sigma^2 \quad [4]$$

for individuals from the original distribution, and

$$\frac{1}{2}h^2\sigma_C^2 \quad [5]$$

for the individuals with $D > 0$. The offspring of mothers with $D > 0$ and fathers from the full distribution inherit one allele from each distribution; the genetic variance of this offspring thus equals the sum of the terms [**4**] and [**5**]. It is likely that environmental heterogeneity stays similar across two generations; we thus assume that the environmental variance remains $(1-h^2)\sigma^2$ in the offspring. The phenotypic variance of the offspring thus is

$$\sigma_C'^2 = \frac{1}{2}h^2\sigma^2 + \frac{1}{2}h^2\sigma_C^2 + (1-h^2)\sigma^2$$

$$= \frac{1}{2}h^2(\sigma^2 + \sigma_C^2) + \sigma_e^2 = 0.88^2. \quad [6]$$

A woman from this distribution has a 5.03% probability of developing FPD in her own childbirth (Fig. 2*B*).

The mothers who delivered vaginally ($D \leq 0$) have a mean of $\mu_V = -2.10$ and SD of $\sigma_V = 0.95$, which follows from the according application of Eqs. **1** and **2**. After random mating, their offspring has a mean of $\mu_V' = -2.07$ and SD $\sigma_V' = 0.99$ (following Eqs. **3** and **6**), which entails an FPD rate of 1.82% (Fig. 2*C*). That is, according to our model, a woman who was born by Caesarean because of FPD shows 2.77 times the risk of developing FPD herself, compared with a woman born vaginally (risk ratio 5.03/1.82 = 2.77).

This predicted risk ratio is independent of the scale of D, the maximum individual fitness, and a constant sexual dimorphism. It is also robust against small deviations of D from normality. The ratio decreases slightly when increasing the initial FPD rate. For instance, raising the initial rate from 2 to 5% decreases the risk ratio from 2.77 to to 2.33. Note that this model refers to the FPD rate, not to the rate of C-sections, which is, of course, much higher and more variable.

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