Original Research Article

Seasonal Modulation of Reproductive Effort During Early Pregnancy in Humans

VIRGINIA J. VITZTHUM,[1*] JONATHAN THORNBURG,[2] AND HILDE SPIELVOGEL[3]
[1]*Anthropology Department & Kinsey Institute for Research in Sex, Gender and Reproduction, Indiana University, Bloomington, Indiana*
[2]*Astronomy Department, Indiana University, Bloomington, Indiana*
[3]*Department of Bioenergetics, Instituto Boliviano de Biología de Altura, Facultad de Medicina, Universidad Mayor de San Andres, La Paz, Bolivia*

ABSTRACT Life history theory predicts that early pregnancy presents a relatively low cost, uncontested opportunity for a woman to terminate investment in a current reproductive opportunity if a conceptus is of poor quality and/or maternal status or environmental conditions are not propitious for a successful birth. We tested this hypothesis in rural Bolivian women experiencing substantial seasonal variation in workload and food resources. Significant risk factors for early pregnancy loss (EPL) included agropastoralism versus other economic strategies, conception during the most arduous seasons versus other seasons, and increasing maternal age. Anovulation rate (AR) was higher during the most arduous seasons and in older women. Breastfeeding and indicators of social status and living conditions did not significantly influence either risk of EPL or AR. Averaged over the year, anovulation occurred in about 1/4 of the cycles and EPL occurred in about 1/3 of the conceptions. This is the first evidence of seasonality of EPL in a non-industrialized population, and the first to demonstrate a relationship between economic activities and EPL. These findings suggest that both anovulation and EPL are potential mechanisms for modulating reproductive effort; such "failures" may also be nonadaptive consequences of conditions hostile to a successful pregnancy. In either case, variation in EPL risk associated with different subsistence activities can be expected to influence fertility levels and birth seasonality in both contemporary and past human populations. These consequences of variability in the risk of EPL can impact efforts to understand the sources of variation in reproductive success. Am. J. Hum. Biol. 21:548–558, 2009.

Early pregnancy loss (EPL) is the most common, yet least understood, fate of a human conception. The rate of EPL (usually defined as terminations occurring prior to ~6 weeks gestation) may be as high as 80% of all fertilized ova (Holman and Wood, 2001; Roberts and Lowe, 1975) yet despite its frequency, the causes of EPL are uncertain (Macklon et al., 2002; Regan and Rai, 2000; Vitzthum, 2008a). Life history theory may be able to explain a large measure of this apparent inefficiency of the human reproductive system.

It is a guiding principle of life history theory that throughout its lifetime an organism faces unavoidable trade-offs in the allocation of finite resources to the competing demands posed by somatic and reproductive processes (Stearns, 1992; Williams, 1966). Effort devoted to somatic growth and maintenance may prolong life but would then not be available for reproduction. On the other hand, a new investment in reproduction can place both one's own survival and future reproductive opportunities at risk. Hence, foregoing a current reproductive opportunity, or terminating one before too much effort has been expended, can be the best life-long strategy.

Thus, many authors have argued that short-term perturbations in women's reproductive functioning (e.g., changes in hormone levels and/or failure to ovulate or failure to maintain a pregnancy) concomitant with energetic or other stressors could be adaptive responses to such challenges (Ellison, 1990, 1994, 2003; Frisch and Revelle, 1970; Jasienska, 2001; Nepomnaschy et al., 2004, 2006; Peacock, 1990, 1991; Prior, 1985a,b, 1987; Vitzthum and Smith, 1989; Vitzthum, 1990, 1997, 2001, 2008a,b; Wasser and Barash, 1983). Although this argument is consistent with evolutionary theory, it has yet to be empirically demonstrated in any human population that such responses to environmental conditions do, in fact, increase relative fitness. Rather, investigators have, of necessity, tested other predictions from these evolutionary models and, if supported, inferred that such disruptions in reproductive effort (RE) are adaptive. This tack has yielded substantial evidence of statistically significant associations between the occurrence of some stressor and changes in the ovarian cycle (see references above and citations within each), but it remains possible that such changes are non-adaptive disruptions of normal functioning.

Perhaps, the most compelling support for adaptive modulation of the probability of conception comes from anthropologists' studies of nonindustrialized populations buffeted by harsh ecological conditions. van der Walt et al. (1978) reported low ovarian steroid levels in !Kung San and suggested that these might be a mechanism to restrict conception to seasons of better nutrition. Notably, the number of births was highest about 9 months after San women had reached their peak body weight. Leslie and Fry (1989) linked the extreme birth seasonality in nomadic Turkana pastoralists to fluctuations in rainfall that drove varying availability of foodstuffs. The highest proportion of conceptions (extrapolated from birth dates) occurred during the period when women's body weight was at its greatest. Studies of the Lese, subsistence farmers in the Ituri Forest, reported declines in body weight

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*Correspondence to: Virginia J. Vitzthum, Anthropology Department, Student Bldg. 130, Indiana University, 701 Kirkwood Ave., Bloomington IN 47405, USA. E-mail: Vitzthum@Indiana.edu

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and the frequency of ovulatory cycles over a 4-month period (Ellison et al., 1989) and an association of periods of low food production and lower body weight with lower salivary progesterone and reduced conception frequency (Bailey et al., 1992). In a Nepalese population observed in winter and again in the more arduous monsoon season, those women who lost weight between the periods also had a significant drop in mid-luteal salivary progesterone (Panter-Brick et al., 1993). A study of Polish agriculturalists reported lower salivary progesterone levels during the months of greatest physical labor compared to hormone levels observed at the end of the harvesting season (Jasienska and Ellison, 1998). In rural Mayan women, increases in cortisol (a marker of energetic, health, and psychosocial stressors) were associated with significantly lower mid-luteal progestin levels (Nepomnaschy et al., 2004).

As demanding as it has been to demonstrate correlations between environmental challenges and indicators of ovarian functioning, it has proven even more difficult to address the question of whether EPL may be, at least in some instances, another adaptive mechanism. Because most conceptions are lost without having been detected in the first place (Holman and Wood, 2001; Vitzthum, 2008a), until recently it was impossible to ascertain whether there are any associations between the risk of EPL and the occurrence of some stressor. The development of sensitive assays for hCG (human chorionic gonadotrophin, produced by the conceptus) afforded the opportunity to detect a conception from about the time of implantation and to follow it through to loss or birth. Several studies have taken advantage of this technology to estimate the rates of EPL and to evaluate which, if any, individual and environmental factors may contribute to this risk (Holman and Wood, 2001; Nepomnaschy et al., 2006; Vitzthum et al., 2006a,b; Wilcox et al., 1990).

It has long been taken for granted that most, if not all, early terminations are attributable to genetic defects in the conceptus (Wood, 1994). This hypothesis derives from cytogenetic studies of recognized pregnancy losses (those occurring later than 6 weeks gestation) and the fact that the proportion of chromosomal abnormalities among pregnancy losses, as well as the risk for pregnancy loss per se, rises with increasing maternal age (such defects are found in 85% of all losses at >40 years maternal age versus 42% of losses at <20 years maternal age) (Wood, 1994). Recent evidence, however, suggests that genetic abnormalities are not necessarily the cause of all but a few EPL. Taken collectively, various studies place the rate of chromosomal abnormalities at about 15% and 8% in human oocytes and spermatozoa, respectively (Pellestor et al., 2005; Templado et al., 2005). Hence, assuming random fertilization and no disfavoring of abnormal gametes, at conception the proportion of abnormal concepti from these causes would be 22%. The risk of EPL is estimated to be at least 50% (Boklage, 1990; Holman and Wood, 2001), leaving a large proportion of pregnancy losses that are not readily attributable to chromosomal defects. Because the oocytes examined for genetic defects were typically from (often older) women undergoing ART, 15% may be an overestimate of the true rate in the larger population. On the other hand, there are an unknown number of genetic defects not detectable with current methods, and the true rate in concepti could be much higher than 22%. Clearly, given the present state of technology and knowledge, it is not possible to state the true rate of genetic defects with precision. Nonetheless, the present evidence suggests that it cannot be assumed that the vast bulk of EPL are necessarily due to genetic abnormalities.

While not dismissing the evident role of genetic defects in EPL, life history theory suggests that the first few weeks of gestation present a relatively uncontested opportunity for a female to terminate investment in the current conceptus if environmental conditions are not propitious for a successful pregnancy. There is some empirical evidence to support this hypothesis.

In a prospective study of nearly 500 noncontracepting married Bangladeshi women, there was no significant age variation in fecundability (the monthly probability of conceiving) but an almost two-fold increase in EPL in 40-year-old women compared to 20-year-olds (Holman and Wood, 2001). In other words, in this impoverished population, age-related variation in RE was a consequence of varying the risk of EPL rather than any variation in hormonal profiles that altered the risk for conception. Although the cause remains unclear, in North Carolinian women, EPL risk peaked during the fall/early winter months in 3 consecutive years (Weinberg et al., 1994). Such seasonality in EPL risk, absent some unknown time-varying cause of genetic defects, suggests modulation of RE in response to maternal and/or environmental factors. Two studies reported hormonal evidence of activation of the HPA (hypothalamic-pituitary-adrenal) axis, which may occur because of psychosocial and/or energetic stressors, in association with an increased risk of EPL. In Guatemalan women, the risk of EPL rose significantly with increases in cortisol levels, apparently a consequence of the demands of daily life (Nepomnaschy et al., 2006). In rural Bolivian women, the follicular phase of conception cycles ending in EPL were characterized by elevated progesterone, most likely of adrenal origin and reflecting transitory but unidentified stressors (Vitzthum et al., 2006a). Although admittedly limited, these studies suggest that early termination may be a low-cost mechanism for modulating RE.

Collectively, the findings from anthropological studies of free-living individuals are consistent with the hypothesis that short-term perturbations in women's reproductive functioning are potentially adaptive in that reductions in RE co-occur with conditions that could have a negative impact on a woman's health status and also on fetal growth and development, and ultimately on infant survivorship. These studies also raise compelling questions regarding which mechanisms for modulating RE are implemented in given circumstances and what the relative adaptive advantage might be of these different responses. Extensive research on the precise causes of exercise associated amenorrhea (the loss of menstrual cycling in some exercising women) suggests that there is a progressive series of adaptive responses to escalating energetic stress beginning with declines in ovarian steroids in the luteal phase and then in the follicular phase, advancing to anovulation, and culminating in amenorrhea (Ellison, 1990; Prior, 1985b, 1987). This dose-dependent relationship is also supported by experimental studies in monkeys (Cameron, 1996).

But among women living in demanding circumstances throughout their lives, a consistent progressive relationship between stressors and changes in reproductive functioning is less evident. In Nepalese women, despite "moderately heavy" energy expenditure in the winter and "very heavy" in the monsoon, only those who lost weight between these two periods showed a significant decline in mid-luteal progesterone (Panter-Brick et al., 1993). In Lese women, those who lost $\geq$2 kg during 4 months averaged lower progesterone levels during this period than those who lost less or gained weight (Ellison et al., 1989). But the ovulation rate did not significantly differ between these 2 groups, even while the rate decreased progressively in the population over the 4 months. In Polish women, differences among women in progesterone levels during the physically demanding summer months were best explained by variation in energy expenditure independent of any change in weight (Jasienska and Ellison, 1998). Why wasn't this effect of demanding physical labor observed in the Nepalese women? What role might unrecognized EPL have played in the patterns of reproductive functioning observed in these populations? As is often the case in science, interesting studies generate intriguing questions. The answers may lie, in part, in evaluating the local environment within which each of these populations is evolving.

In the context of a natural fertility nonindustrialized population in which most adult women are in heterosexual partnerships, it could be evolutionarily advantageous for a woman to conceive (even if the probability of successful reproduction is uncertain) rather than "choose" anovulation (an irreversible rejection of a current opportunity to reproduce). With early termination as a potential modulation mechanism, a woman would gain additional time and information, with little cost in either lost time or resources, to ascertain whether the present RE is a viable option. This decision cannot be delayed for very long, however, because waiting would increase opportunity costs and because, over time, developing fetal-defense mechanisms increasingly constrain maternal options (Nepomnaschy et al., 2006; Vitzthum, 2008a).

As a first step in evaluating the relative roles of different mechanisms for terminating RE in a current opportunity, we compare the risks of anovulation and EPL, and test several hypotheses regarding the risk factors for each mechanism, throughout a single year in a rural Bolivian population. We have previously demonstrated that successful conceptions (those that resulted in a term birth) occurred in this population at progesterone levels only about 70% those of U.S. women (Vitzthum et al., 2004) and that EPL was associated with a rise in follicular-phase (adrenal) progesterone (Vitzthum et al., 2006a). Here, we consider the effects of maternal age, living conditions, sociocultural status, breastfeeding, and agropastoral labor on the risks of anovulation and EPL. The present analyses will clarify the contributions of anovulation and pregnancy termination to the modulation of RE in these women.

METHODS AND MATERIALS

The data used in these analyses are from Project REPA (Reproduction and Ecology in Provincia Aroma), a multidisciplinary longitudinal study of reproductive functioning and health in rural Bolivian women (Vitzthum et al., 2000a,b, 2001, 2002, 2004, 2006a,b), designed to test predictions of the Flexible Response Model (Vitzthum, 1990, 1997, 2001) and implemented in cooperation with the Instituto Boliviano de Biología de Altura in La Paz, Bolivia. The study design was adapted from the North Carolina Early Pregnancy Study (Wilcox et al., 1988; Wood 1994, p. 243). Preliminary work began in 1989, followed by more than 2 years of continuous fieldwork from 1995 to 1997.

Study population and participants

Study participants were recruited during 12 months beginning in November 1995 and represented more than 80% of the eligible women in 30 communities scattered over 200 km^2 situated about mid-way between La Paz and Oruro. Inclusion criteria included falling within 20–40 years of age, currently in a stable heterosexual union, and not using contraception. To avoid selection bias (Vitzthum, 2008b), women were recruited without regard to current reproductive status. Of 316 adult female participants, 125 were pregnant and/or lactating and noncycling at recruitment and throughout the study, 98 were lactating at the time of the first observed menstrual segment, and 93 were menstruating/not-breastfeeding at recruitment. All study protocols were approved by the Institutional Review Board, University of California, Riverside.

Analytical samples

The collection protocol for ovarian cycle data has been previously described (Vitzthum et al., 2000b, 2001, 2004, 2006a). In brief, throughout participation menstruating women (n = 191) were visited every other day to record menstrual status and collect a 5 ml saliva sample, later assayed for progesterone. Beginning at 24–25 days following each first day of menstrual bleeding, a urine sample was tested for hCG using a commercial pregnancy test (StanBio [Boerne, TX] QuPID, sensitive at 25 IU/L hCG; accuracy > 99%, specificity > 99%). Because of the isolated conditions and lack of electricity, urine samples could not be frozen for more sensitive laboratory testing at some later time. Urine collection continued every other day until the next menses or, in the case of a positive test, until pregnancy loss or the sixth month of gestation.

Of 612 menstrual cycles with a known outcome (in 166 women, 1–8 cycles/woman, median = 4 cycles/woman), 65 were associated with at least one positive hCG test, of which 52 were associated with at least two positive tests (given the test's high accuracy and specificity, it is virtually impossible for the 13 cycles with one positive test to be all false positives; discussion with a StanBio technician suggested it is very unlikely that there was more than one false positive). Of the 65 putative conceptions, 23 were observed to term, 27 were lost before the third trimester, 1 was medically aborted, and 14 women withdrew from the study while still pregnant, principally due to waning participant interest. The timing of pregnancy loss was defined as the first day of vaginal bleeding following a positive hCG test (if subsequently confirmed by sequential negative hCG tests). EPL was defined as those conceptions terminating prior to the 7th week from the first day of the last menstrual period (LMP) (Vitzthum et al., 2006a), about the time when the placental production of progesterone exceeds that originating from the corpus luteum (Lenton, 1988). Of the 65 conceptions (observed in 63 women), 18 (in 17 women) were classified as EPL. Sustained conceptions (SC, n = 40 in 39 women) were those persisting >7 weeks post-LMP. Pregnant women with-

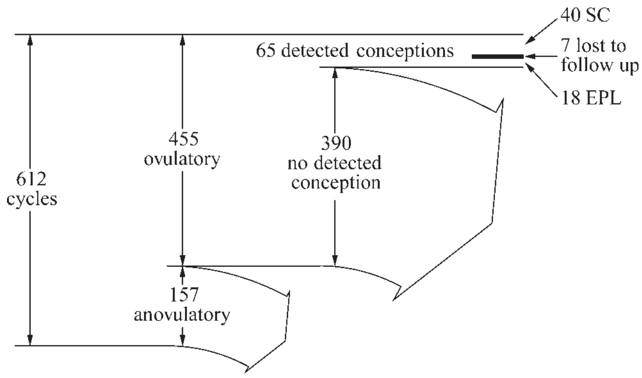


Fig. 1. Known outcomes of 612 cycles observed during 1996 in 166 women participating in Project REPA. EPL, early pregnancy loss; SC, sustained conceptions.

drawing prior to 7 weeks post-LMP ($n = 7$) were not included in either sample. In each of two women, the second observed conception is not statistically independent from her first observed conception and was not included in any statistical analyses.

Although a luteal rise in progesterone is characteristic of normal ovulation, there is no definitive threshold of salivary progesterone below which ovulation can be said not to have occurred. This study uses a previously described algorithm to distinguish ovulatory from nonovulatory cycles (Vitzthum et al., 2004). In brief, to be considered ovulatory a nonconception cycle must have a mean-peak-luteal progesterone level both greater than its mean-peak-follicular progesterone level and >110 pmol/l. All conception cycles are, of course, also ovulatory. Of 612 cycles, 455 could be classified as ovulatory and 157 as anovulatory (see Fig. 1).

Individual, household, and environmental variables

Data on a wide range of factors that might influence female reproductive functioning were collected in a series of private, structured interviews conducted by a trained female bilingual (Spanish/Aymara) Bolivian field assistant (a *promotora*) in a woman's native language over the course of her participation in the study. The series of interview instruments requested information of a progressively more personal nature, and repeated some questions to allow the cross-checking of prior answers. Each *promotora* took care to establish a positive relationship with "her" participants (with whom she averaged about 50 visits/participant), and nearly all women answered most of the interview questions.

The ages of all family members were verified with documentation (identity cards, birth and marriage certificates) whenever possible. In all cases, adult women's ages could be determined within 1 year. Indicators of sociocultural status included first language (Aymara or Spanish) and skill level in any second language, dress style (traditional or modern), and years of education. Indicators of living conditions included several aspects of house construction and size; water sources and sanitation facilities; and fuel types for lighting, heating, and cooking. Economic indicators included property holdings, crops planted, animals owned, and sources of monetary income; regular income was defined as securing cash for labor or goods on a weekly or daily basis throughout most of the year.

The planting (late-winter/early-spring, before the summer rains begin) and harvesting (late rain through autumn) seasons are physically more demanding than winter and summer (the rainy season when crops are growing). Late autumn, when more attention is given to processing harvested crops in preparation for winter storage, is less physically demanding than the earlier weeks of peak harvesting. Food resources are relatively lower during the late-rain/early-harvest and late-winter/planting periods (when stored foods are more depleted) and are more abundant during the late-harvest and early-winter periods. Based on weather data (NOAA, 2008) and observations and reports collected throughout 1996, seasons are defined as late-rain/early-harvest (through end of March, days of year = 1–91), late-harvest (through mid-May, days of year = 92-136), winter (through end of August, days of year = 137–244), planting (through early October, days of year = 245–282), early-rain (through end of year, days of year = 283–366). For these analyses, the most energetically demanding periods, when food availability is relatively lower *and* labor demands are relatively higher (i.e., late-rain/early-harvest [days 1–91] and planting [days 245–282]), are defined as "arduous" seasons compared to the rest of the year ("better" seasons). This distinction is relative; even during better seasons, life is demanding in these *altiplano* communities.

Statistical approach

We used SPSS version 16.0 for Windows for statistical analyses. We evaluated differences between subsamples of the study sample with either a χ^2 test (categorical variables) or a t-test (continuous variables); $P \leq 0.05$ was considered statistically significant. Bootstrapping and moving averages were done with custom-written software. In Figure 2, moving averages of risk for anovulation and of risk for EPL (left-hand axis) and temperature and rainfall (right-hand axes) were plotted against season (x-axis) and day of year (top axis).

Relative risk (RR) for EPL and its 95% confidence interval (CI) was calculated for the dichotomous states of each categorical variable. RR was estimated for continuous variables using univariate logistic regression models (Petrie and Sabin, 2005). Fisher's exact test was used to evaluate the risk of EPL in the case of an empty cell (i.e., no observed EPL in a defined subsample). To control for the effect of potential covariates, putative risk factors were also evaluated with multivariate logistic regression models; the odds ratio (OR) specific to a factor is an estimate of the RR for EPL while adjusting for all other factors included in the model (Petrie and Sabin, 2005). Multivariate logistic regression, evaluated with the Wald statistic (estimates significance of each variable in a model) and the Hosmer and Lemeshow (1989) test for goodness of fit (a higher statistic indicates a better fit of the model to the data), was used to determine the "best" models fitting the data.

The anovulation rate (AR, number of anovulatory cycles/total number of cycles) was calculated for each woman for the entire year (AR_T) and for the "arduous" (AR_A) and "better" (AR_B) seasons. Differences in AR_T for the dichotomous states of each categorical variable (e.g., breastfeeding vs. not breastfeeding, has latrine vs. no la-

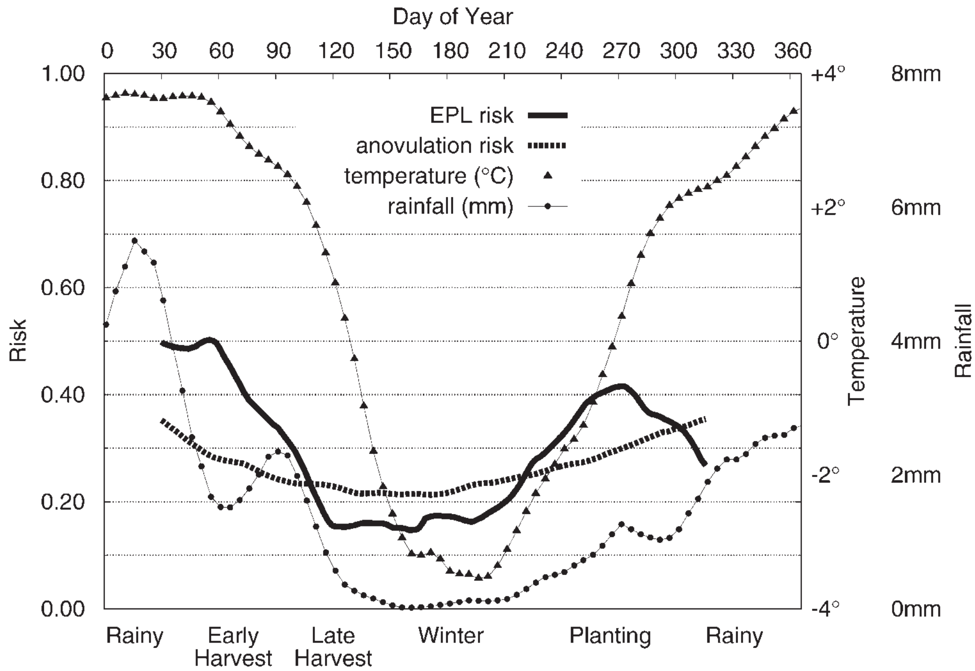


Fig. 2. Risk of anovulation and EPL (left-hand scale), and daily rainfall (far right-hand scale) and minimum-temperature (near right-hand scale), as functions of time (top scale, day of year). Agricultural activities (bottom scale) are positioned relative to day of year. The data were smoothed using triangular moving-average windows of duration ±60 days for the EPL and anovulation risks and ±30 days for the weather data. Weather data are for 1996 from the weather station (La Paz) closest to the study region (NOAA, 2008). Risk of EPL and anovulation are elevated during the most energetically demanding periods.

trine) were evaluated with a Mann–Whitney *U* Test. The statistical significance of the observed RR_{AB} for anovulation in arduous versus better seasons ($= AR_A/AR_B$) was evaluated using bootstrapping (Efron and Gong, 1983; Efron and Tibshirani, 1996). For each of 100,000 iterations, 612 cycles were randomly selected with replacement from the sample of 612 observed cycles; AR_A, AR_B, and RR_{AB} for anovulation were calculated. The proportion of runs generating a $RR_{AB} \leq 1.0$ gives the significance level of the observed RR_{AB}. In addition, the same bootstrapping approach was applied to evaluate the statistical significance of RR_{HL} ($= AR_H/AR_L$) where AR_L was defined as the period from April 1 through August 31 (autumn through winter, during which the risk of anovulation is visibly lowest, Fig. 2) and AR_H is the remainder of the year (during which the risk of anovulation is higher).

RESULTS

Principal attributes of sample

Table 1 lists those individual and socioeconomic indicators that varied among the women and, hence, might be risk factors for variation in anovulation rate and conception outcome.

TABLE 1. Principal attributes of study sample

Indicator	% of sample
Women	
Age	mean = 29.2 years, SD = 4.9
Education	median = 5 years, range = 0–13 years
Breastfeeding	51%
Poor skills in spoken Spanish	30%
Primary occupation is agropastoralist	51%
Has regular monetary income	40%
Women's husbands	
Primary occupation is agropastoralist	46%
Primary job is in city	34%
Has regular monetary income	60%
Living conditions	
Owns farm	59%
One-room dwelling	23%
Only oven is outside	53%
No latrine	58%
Relies on public water source	48%
Wood is only fuel	14%
Gas is only fuel	33%
No electricity	52%
Owns vehicle	6%

Individual characteristics. Mean age was 29.2 years (median = 30 years, range = 20-38 years). All women drank coffee every morning, none smoked tobacco, and none drank alcohol or chewed coca other than on rare occasions (e.g., fiestas, rituals). About half of the women were breastfeeding. The median years of schooling was 5 (i.e., through completion of primary school [*basico*]). Aymara was the first language for nearly all women, but most also had at least a moderate command of spoken Spanish. Women preferred wearing traditional clothing (*de pollera*: several layers of petticoats/skirts and shirts/blouses/cardigans/shawls, open sandals or flat shoes, and a hat, but not stockings or gloves). In contrast, virtually all men wore modern clothing, most often with sandals (without socks), and had a good to excellent command of Spanish, as much due to compulsory military service as to schooling.

Living conditions. Most couples (86%) owned their home. Dwelling space was typically 1, 2, or 3 rooms (roughly 30% of the sample in each dwelling size), all at ground level. Virtually all homes were of adobe, most with wooden floors (some had floors of pounded dirt or of cement) and tin roofs (occasionally of straw). A few couples had as many as five rooms, some of which might be located on an upper floor. Most households used both wood and pressurized propane for cooking. The poorest farm dwellers relied only on wood; the poorest nonfarmers, living in a rented room, used propane. Because wood requires considerable labor to collect and propane must be purchased, fuel was very rarely used solely for heating. About half the households lacked electricity, but even when theoretically available, electrical service was intermittent at best. Only slightly more than half the households had access to private water sources (wells and/or faucets). The remainder relied on public wells, the river, and canals, which typically required hauling water long distances, most often by foot. The majority of households did not have access to latrines, instead using "*el campo abierto*" (the open countryside) for sanitation.

Economic activities. In addition to caring for their homes and families, agropastoralism was the primary occupation for about half of these women, the rest earning their living principally through selling goods or their own crafts, or sporadically hiring out their labor. Most agropastoralists also sold agricultural products, but only about a third did so regularly. Only five women considered themselves to be housewives without an additional occupation.

Their husbands' economic activities were more varied. Agropastoralism was the primary occupation for less than half of these men. About a fourth were hired laborers (construction, factory, and caretaker), the remainder comprising a few drivers (truck/bus/taxi), public servants, teachers, and craftsmen. However, as "multitasking" is a common economic strategy, nearly 60% of all husbands were actively engaged in agropastoralism. About a third worked solely or principally in a major city, most returning home each weekend. Although 60% of husbands indicated earning regular monetary income, almost none of the men (other than a few agropastoralists who sold their milk daily to the country's largest dairy marketer) ever sold agricultural products or goods of any kind.

The majority of couples owned and worked a farm, done almost entirely by hand. On many farms, even plowing was done without an animal to help pull. In general, all farmers had the same crops (barley, potatoes, wheat, fava beans, and onions, in decreasing order of commonness); farm acreage and/or production levels were not generally divulged to the study team. Most farms had sheep and cows, but about half were without any mule (none had a horse); less than half had chickens and/or pigs. With the exception of two households that each kept a pig, none of the nonfarmers owned any animals.

Early pregnancy loss

There is substantial seasonality in EPL risk (see Fig. 2). Figure 3 (top panel) depicts RR (and its 95%CI) for individual putative risk factors (all risk factors found to be significant are listed; variation in sample sizes reflects participant willingness to answer questions). For each dichotomous categorical variable, RR is the increase in EPL risk for having State 2 instead of State 1. For continuous variables, RR is the increase in EPL risk for each increase of the variable by 1 unit (decade for maternal age, year for education). All putative risk factors were also evaluated by logistic regression while holding constant maternal-age and/or conception-season and/or owns-farm. Of these latter analyses, Figure 3 (bottom panel) presents the best models explaining the risk of EPL.

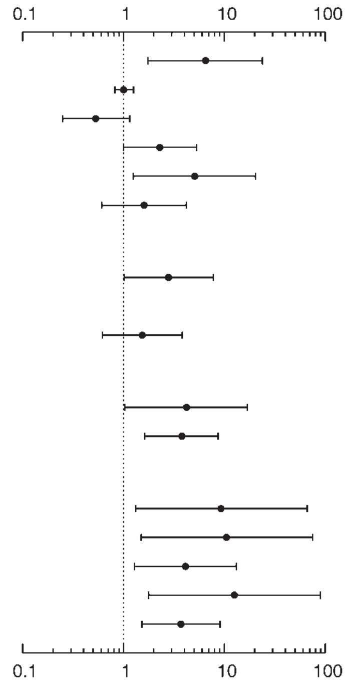
The largest risk factors for EPL were related to agropastoralism (Fig. 3, top: owns-farm, grows-barley, grows-wheat, owns-sheep, agropastoralism is primary occupation of either partner). The univariate RR of these indicators ranged from 2.8 to 12.6, and in every case (except husband's primary occupation) the lower 95%CL was well above 1.0. All agropastoral indictors were strongly co-linear, though not necessarily reaching identity (e.g., not all farms have sheep; any man owning sheep also owns a farm, but his primary occupation may not be agropastoralism). In subsequent multivariate analyses, owns-farm [RR = 9.3, 95%CI: 1.3–66.2] was selected as the best single indicator of agropastoralism because (1) this variable was known for the largest number of participants, and (2) in bivariate stepwise logistic regression, owns-farm was included in the model preferentially to any other agropastoral variable.

Conception during arduous seasons (RR = 3.7, 95%CI: 1.5–9.1), and increasing maternal age (odds ratio: OR/decade = 6.5, 95%CI: 1.7–23.9) were also significant univariate risk factors for EPL. In addition, the wives of those men who worked principally in the city did not experience any observed EPL, compared to a 37% rate of EPL if the husband worked principally in his own community (Fisher's exact test, two-sided $P = 0.02$).

The best-fitting multivariate logistic regression model (Fig. 3, bottom panel) included only conception-season (adjusted OR = 14.5, 95%CI: 2.3–93) and owns-farm (adjusted OR = 34.4, 95%CI: 2.9–407). The model with the highest Nagelkerke r^2 (Model 2) included maternal age (adjusted OR = 11.2, 95%CI: 0.95–131), conception-season (adjusted OR = 34.8, 95%CI: 2.4–506), and owns-farm (adjusted OR = 26.2, 95%CI: 1.8–388). The 95%CI are broad, a reflection of the small sample of EPL. Nonetheless, even with this small sample, the effects of agropastoralism and conception are sufficiently great such that the lower bound of the 95%CI is well above 1 for both variables. The 95%CI for maternal age encompasses one in several of the analyses. This outcome is most likely the consequence of the limited age range of the sample (none of the women are older than 38 years). Rather than inferring that maternal age has no significant effect on EPL risk in this sample (unlikely given strong evidence to the contrary; Holman and Wood, 2001), it is more likely that the effect is relatively modest during the age range of these women.

In this sample of conceiving women, farm-owners and nonfarmers differed in more than just economic strategies. All but one farming couple owned their home whereas 25% of nonfarmers did not ($P = 0.037$). Most farmers (88%) had only one oven, located outside their house, while most nonfarmers (85%) had an oven within the home ($P = 0.0001$). Nonfarmers were more likely to have electricity (75% vs. 33%, $P = 0.003$) and access to private water sources (76% vs. 37%, $P = 0.007$), but comparable proportions (about 60%) lacked access to latrines. Regular income was much less common among farmers than

	State 1	EPL/N	State 2	EPL/N
Conceiving Woman:				
Age in decades (continuous[1])				
Years education[2] (continuous[1])				
Breastfeeding at conception[2]	No	8/18	Yes	9/38
Spanish skills[2]	Good	8/37	Poor	6/12
Primary occupation[3]	Other	2/23	Agropastoral	11/25
Regular monetary income[2]	Yes	5/19	No	8/24
Woman's Husband:				
Primary occupation[3]	Other	4/25	Agropastoral	9/20
Primary work location (p=0.02)[4]	City	0/11	Community	13/35
Regular monetary income[2]	Yes	8/32	No	5/13
Living Conditions:				
Only oven is outside[2]	No	2/20	Yes	10/24
Uses only wood for fuel[2]	No	8/40	Yes	3/4
Agropastoral Indicators:[3]				
Owns farm	No	1/21	Yes	12/27
Grows barley	No	1/22	Yes	11/23
Grows wheat	No	3/26	Yes	9/19
Owns sheep	No	1/24	Yes	11/21
Conception season[5]	Better	5/34	Arduous	12/22



	r^2	H-L fit	Wald p	State1	EPL/N	State2	EPL/N
Model 1	0.52	0.93					
Conception season			0.005	Better	5/34	Arduous	12/22
Owns farm			0.005	No	1/21	Yes	12/27
Model 2	0.62	0.14					
Maternal age (decades)			0.055				
Conception season			0.009	Better	5/34	Arduous	12/22
Owns farm			0.018	No	1/21	Yes	12/27
Model 3	0.45	0.009					
Maternal age (decades)			0.005				
Conception season			0.002	Better	5/34	Arduous	12/22
Model 4	0.38	0.16					
Maternal age (decades)			0.081				
Owns farm			0.039	No	1/21	Yes	12/27

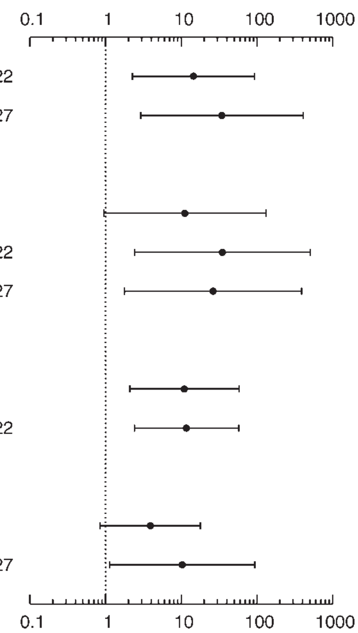


Fig. 3. Top Panel: Univariate relative risk (RR) and its 95%CI (plotted on log scale) for each factor (State 2 compared to State 1). EPL/N is number of losses/number of individuals for given state of a factor. [1]RR estimated by odds ratio from logistic regression. [2]If covariates (maternal-age, owns-farm, conception-season) are held constant, RR is not significant. [3]See bottom panel for multivariate analyses. [4]Maternal-age does not differ ($P > 0.30$) by husband's-work-location. [5]Arduous seasons are more energetically demanding; better seasons are all other periods; see text for additional explanation. Bottom panel: multivariate logistic regression models. Odds ratio and its 95%CI (plotted on log scale) for each factor (State 2 compared to State 1). EPL/N is number of losses/number of individuals for given state of a factor. r^2 = Nagelkerke r^2 for full model, H-L fit = Hosmer and Lemeshow test for goodness of fit (range = 0–1; 1 = best fitting model), Wald p = Wald significance for each variable in model.

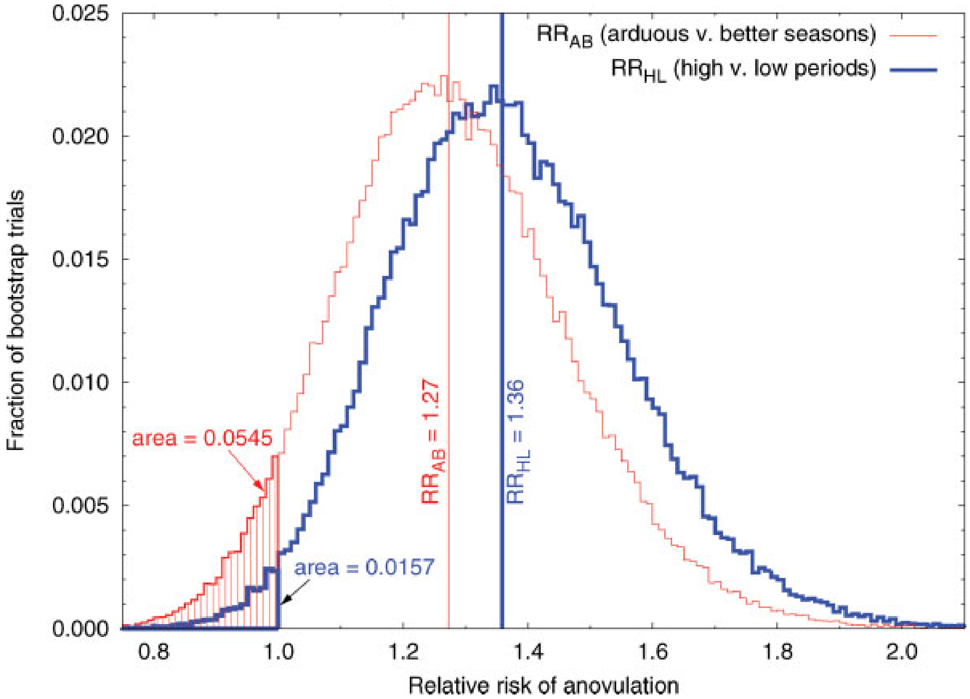


Fig. 4. Distribution of 100,000 bootstrap iterations for relative risk (RR) of anovulation in arduous versus better seasons (RR_{AB}, thin line) and high v. low periods (RR_{HL}, thick line). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

non-farmers (women: 37% vs. 67%, $P = 0.042$; husbands: 56% vs. 94%, $P = 0.005$). All nonfarming women had at least a moderate command of spoken Spanish, but 40% of the farm women had only poor skills ($P = 0.001$). Maternal age in farm-owners was significantly older than that of those women not owning farms (30.0 years [s.d = 5.4] vs. 25.9 years [s.d. = 4.3], $P = 0.007$), but owns-farm was still a significant risk factor for EPL even after controlling for maternal age (Fig. 3, bottom). There was no difference between the two economic groups in the proportion of conceptions that occurred in different seasons. Nor, within each economic group or for the entire sample of conceptions, was there an age difference between women conceiving in different seasons.

Breastfeeding at the time of conception, maternal education level or language skills, living conditions, and indicators of monetary income did not significantly influence pregnancy outcome once maternal-age, owns-farm, and/or conception-season were held constant.

Anovulation rate

The moving average for AR (see Fig. 2) varies seasonally, the lowest risk occurring during winter and higher risks during the most arduous seasons. The observed RR_{AB} for anovulation in arduous versus better seasons was 1.27 ($P = 0.0545$, based on 100,000 bootstrap iterations; Fig. 4). The observed RR_{HL} for anovulation was 1.36 ($P = 0.0157$, based on 100,000 bootstrap iterations; Fig. 4).

Women's age is the only other significant risk factor for anovulation. In women $\geq$30 years old ($n = 88$) compared to those <30 years old ($n = 78$), all of the observed cycles were anovulatory in 15% versus 6.8%, at least half of the observed cycles were anovulatory in 28% versus 17%, and none of the observed cycles were anovulatory in 40% versus 53%, respectively. Median AR_T for all women = 0.167, for women $\geq$30 years old = 0.2, and for woman <30 = 0. The difference in AR_T between older and younger women was significant (Mann–Whitney U, $P = 0.024$). AR did not vary significantly with whether or not a menstruating woman was also breastfeeding, neither with a woman's education, language skills, or living conditions, nor with any of the economic indicators.

DISCUSSION

These findings suggest that varying the risks of anovulation and EPL are both important mechanisms for modulating reproductive effort in these rural Bolivian women. By far, the most common fate of an initiated cycle is ovulation without conception, anovulation being next (see Fig. 1). Yet, even though early termination is the least likely outcome overall, it occurs in about a third of the observed conceptions. In other words, for each context-specific "decision" regarding whether to irrevocably terminate RE in the current opportunity, anovulation occurred about one-fourth of the time, and EPL occurred about one-third of the time, over the course of the year. Even though anovulation and EPL are usually unrecognized, neither is necessarily insignificant.

To our knowledge, this is the first study to report seasonality of EPL in a nonindustrialized population and the first to demonstrate a relationship between economic activities and EPL. The risk for EPL during the most arduous seasons was 3.7 times that of better seasons, and the risk for EPL in farm owners was 9 times that for non-farmers. The minimum risk was 0.15 on day 160 and the maximum risk was 0.50 on day 55 (see Fig. 2). Unquestionably, as in all other studies of early pregnancy loss, there were lost conceptions that went entirely undetected because of a technical inability to identify conceptions lost before implantation or before a detectable rise in hCG. Nonetheless, the minimum risk in the present study did not differ much from the estimates of expected losses (~22%) predicted from a determination of chromosomal abnormalities in human oocytes and spermatozoa (Pellestor et al., 2005; Templado et al., 2005), and the range of EPL risk was comparable to that observed in a study of North Carolinian women (Weinberg et al., 1994).

Although the greatest risk for EPL in this population occurred among agropastoralists during the most physically demanding periods, energetic demands are not the only challenges faced by these women. In the Bolivian highlands, respiratory and gastrointestinal infections are widespread, but rural farmers have limited access to biomedical health care. There is some evidence that pregnancy loss is elevated in circumstances or seasons in which infection rates are relatively greater. Malaria appears to have contributed to the high risk of pregnancy loss in settled Turkana pastoralists (DeLuca, 1997; Leslie et al., 1993; Little and Leslie, 1999), and increased risk of infectious disease may also explain elevated loss of clinically recognized pregnancies in industrialized populations (Kaplan, 1973; McDonald, 1971). In the only other study to report seasonality in EPL, North Carolinian women were observed to have a greater risk of EPL during the fall/early winter months (Weinberg et al., 1994), but no reason for the pattern was discernable. An explanation, at least in part, may be a seasonal rise in the risk of infection, but this hypothesis remains to be tested.

Agropastoral women in this population may also experience more psychosocial stress than nonfarming women. An association between greater risk of EPL and high scores of psychological distress was observed in Danish women (Hjollund et al., 1999), and the risk of EPL in Guatemalan women rose with increases in cortisol, a stress biomarker (Nepomnaschy et al., 2006). In the Bolivian highlands, daily life is, to say the least, daunting. The weather can be unpredictable yet planting must be completed before the rains start, harvesting before the crops freeze. Adequate grazing sites for sheep and cows must be located every day, and fodder stored for winter. Agropastoral homesteads are typically isolated, the most common transportation by foot. If illness, accident, violence or some emergency occurs, it can be nearly impossible to secure aid quickly from a neighbor or any authority. Because many agropastoral women have poor Spanish-language skills, they often have difficulty negotiating the byzantine bureaucracies at schools and health posts. Most personnel at these institutions do not speak Aymara, and many openly display their hostility to indigenous peoples. Agropastoralists are much less likely to have regular monetary income, yet no family can do without at least some cash for numerous small and large necessities (e.g., cooking oil, medicines). Although nearly all own their homes and farms, there is nothing secure about the lives of agropastoralists in the Bolivian *altiplano*. Nonetheless, further study is necessary to determine if psychosocial stress raises the risk of EPL in these women.

Given the potential incompatibility of investment in two offspring, it is somewhat surprising that breastfeeding at the time of conception did not increase EPL risk. However, the pattern and intensity of breastfeeding were not evaluated; breastfeeding coincident with a new conception may have been only occasional succorance without a significant energetic demand on mothers. Also, women able to conceive while breastfeeding may have had sufficiently adequate nutritional reserves to manage both investments, at least for a time. Although the total energetic costs of producing a live birth are quite high, these are not distributed equally throughout gestation; there is no evidence that the energy requirements of early pregnancy are particularly demanding (Dufour and Sauther, 2002).

Although agropastoralists were less likely to earn regular monetary income, this economic indicator was not a risk factor for EPL. Perhaps this indicator was too crude a measure of the variation among households in available cash. In addition, those with regular income pursued a variety of economic strategies. Most agropastoralists acquired cash by selling their own farm products (e.g., milk, crops, wool); earning income on a regular basis may have required working even harder to generate a surplus for sale. Nonfarmers, however, often earned money by less laborious employment. It is intriguing that there were no EPL among the 11 conceptions in women whose husbands worked principally in the city (four of whom also had farms). In contrast, there were 13 EPL in the 35 conceptions among women whose husbands worked in their own communities. While a husband's absence might increase some women's labor, especially among agropastoralists, perhaps higher city wages offset this additional burden (e.g., purchased foodstuffs). Similarly, the lost companionship could exacerbate a woman's psychosocial stress but might also mitigate spousal violence, a common if undocumented danger endured by many women in these communities. Unfortunately, the available data and sample size were not amenable to investigating such subtleties in economic strategies and behaviors.

The minimum risk for anovulation = 0.21 on day 171, and the maximum risk = 0.35 on days 30 and 315 (see Fig. 2). Both rates were higher than those observed in cross-sectional samples of Chicago women (9%) and better-off urban Bolivian women (12%), but lower than that of poor peri-urban Bolivian women (55%) (Vitzthum et al., 2002). With the caveat that it is difficult to compare AR across studies because of the different criteria used to ascribe ovulation (Vitzthum, 2008b), the AR was 0.30 for Lese women (Ellison et al., 1989) and 0.47 in a sample of healthy Finish university students (Vuorento et al., 1989).

The RR_{AB} for anovulation during the most arduous seasons was 1.27 relative to better periods. Comparing the periods of highest risk to that of lowest risk, RR_{HL} was 1.36. Seasonality in AR has also been reported for the Lese (Ellison et al., 1989) and the Tamang (Panter-Brick et al., 1993). Much like the rural Bolivians, both of these populations rely principally on subsistence agriculture and experience seasonal variation in available food resources and labor demands.

Maternal age was the only other examined factor that explained variation in AR in these Bolivian women. Increasing maternal age was also a risk factor for EPL. These observations are consistent with those of many other studies in both industrialized and non-industrialized populations (Holman and Wood, 2001; Vitzthum, 2008a,b). It has been widely thought that age-associated increases in AR and EPL reflect senescence of the HPO-axis and deterioration of the aging ovum. However, another (nonexclusive) hypothesis that has not received sufficient consideration is that changes in maternal condition that occur with aging may make pregnancy more risky and, hence, may make it advantageous for a woman to be more discriminating in her investment in new opportunities as she ages.

The demonstration of EPL seasonality has implications beyond life history theory. For uncertain reasons, there is regionally diverse seasonality in human birth rates (Lam and Miron, 1994). Populational variation in the causes and timing of EPL may be contributing to this seasonality and confounding efforts to understand its causes. It has also been suggested that the adoption of agriculture prompted population growth by ensuring a more stable food supply than did foraging strategies and/or by creating weaning foods, thereby shortening postpartum subfecundity (Sellen and Mace, 1997; Sellen and Smay, 2001). Our findings suggest that arduous labor, or some other attribute characterizing at least some agricultural regimes, can increase the risk of EPL, which lengthens the interbirth interval and reduces fertility. This potential consequence of more laborious subsistence practices may explain some of the variation seen in fertility levels among agricultural populations and cautions against expecting that the adoption of agriculture inevitably leads to higher fertility. Our results also challenge the prevailing opinion that most EPL arise from genetic abnormalities (and hence would be expected to occur at a fairly constant rate over time) and suggest that investigations into the effects of maternal activity patterns and other potential environmental stressors are promising avenues of research for better understanding the etiology of EPL.

From a life history perspective, it is intriguing that there was a greater risk of EPL than of anovulation during the two most arduous seasons (see Fig. 2) but a relatively lower risk during the winter months. In addition, seasonal modulation in EPL risk was much larger than that in anovulation risk (a factor of 3.7 vs. 1.36 over the course of the year). These patterns are consistent with the hypothesis that EPL, like anovulation, is an important low-cost mechanism for maternal termination of RE in a current opportunity and, furthermore, suggest that early termination is not merely a back-up plan during periods when the risk of anovulation is low. It has been recognized for some time that EPL can be a mechanism for terminating investment in an offspring of poor quality (Baird et al., 1991; Haig, 1990, 1993). Accumulating evidence suggests that it is also likely to be a mechanism for modulating RE when maternal condition and/or available social and material resources are not propitious for successful reproduction. EPL is adaptive if continued investment in the lost pregnancy would have resulted in relatively lower lifetime reproductive success than not doing so. This evolutionary hypothesis is both logical and consistent with observations in some other species (Stearns, 1992). Definitive tests for the operation of such a life history strategy in humans, however, remain elusive.

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