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by

Darryl J. Holman
University of Washington

James W. Wood
University of Washington

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Darryl J. Holman[1] and James W. Wood[2]

[1]Department of Anthropology
Center for Studies in Demography and Ecology
University of Washington
Seattle, WA 98195, USA.

[2]Department of Anthropology
Population Research Institute
Pennsylvania State University
University Park, PA 16802, USA

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Compared to other mammals, reproduction in women is characterized by low lifetime fertility, a slow pace of reproduction, and a large investment in each offspring. The reproductive span begins relatively late in life; births tend to be spaced at increasingly longer intervals until they stop altogether. Many women then live well beyond ages at which reproduction is possible, something that is rarely seen in other mammals. Making sense out of this pattern of reproduction has been a goal of anthropologists, demographers, physiologists, and evolutionary biologists.

In this chapter, we examine one aspect of this pattern: the way that births are spaced across the female reproductive life span. The timing of births is a complex outcome of many physiological, cultural, and behavioral factors, but our focus will be on two of the components that play an important role in shaping female fecundity and birthspacing. These components are pregnancy loss, which is defined as the loss of any product of conception prior to birth, and fecundability, defined as the monthly or cycle wise probability of conception. We pay particular attention to some of the methodological difficulties that are encountered in trying to measure fecundability and pregnancy loss, and how these difficulties have limited or distorted our understanding of age related changes in female fecundity. We propose new methods to overcome the difficulties and apply the methods to data collected in rural Bangladesh.

The physiological changes associated with menarche and menopause explain much of the lower levels of natural fertility at the extremes of the reproductive span. Between these two points substantial changes in fertility can be observed as an increase in the average length of birth intervals. A universal finding from studies among natural fertility populations is that female fecundity initially increases to a peak in the early 20s and then declines by a woman's age.[1] These age related changes in birthspacing can be fruitfully explored by dividing the reproductive life course into a series of smaller components. (Figure 1). At the top level, the reproductive life course is a series of events including menarche, menopause and a number of birth intervals. The time from marriage to first birth defines the first birth interval, and each subsequent birth defines the start of a new birth interval. Each birth interval can be subdivided into four meaningful events separated by three waiting times (Figure 1, row 2). A live birth is followed by a waiting time until the return of fecundity. This is followed by a *fecund waiting time* to the next conception, which is some number of months or menstrual cycles until a conception occurs. Finally, a conception is followed by a period of gestation which, in the absence of pregnancy loss, terminates in a live birth.

The role that pregnancy loss plays in shaping birth intervals can be understood from the third row of Figure 1. At the time a pregnancy is lost, some period of gestation leading up to that point has been added to the current birth interval. The distribution of these partial gestations is determined by the gestational age-specific risk (or hazard) of pregnancy loss.

[1] Natural fertility populations are those in which effective methods of contraception are not used to limit reproduction. See Wood (1994) for a technical definition and discussion of the concept of natural fertility. Natural fertility populations provide an ideal experimental system in which to examine the physiological and behavioral components of human birthspacing (Henry 1961). For this reason, discussions of the reproductive life course and components of birthspacing in this paper are restricted to conditions of natural fertility.

After a pregnancy is lost, three new waiting times are added to the birth interval. The first is a *post loss nonsusceptible wait*, which is a period of time in which a woman is not susceptible to conception. A pregnancy lost immediately after conception will add little to this waiting time. Wilcox et al. (1988) gives the lengths of menstrual cycles following 43 sub-clinical pregnancy losses that were detected, on average, by day 11. Menstrual cycles were lengthened by an average of two days, which represents the *combined* effects of the length of gestation that preceded the loss and any delays added through the follicular phase of the following cycle. One third of the subjects who experienced an early pregnancy losses conceived in the next cycle (compared to 25 percent for the study on the whole), so that it appears that these early losses do not lead to a high probability of anovulation in the following cycles. Studies of resumption of menses in women who never breast feed provide information about the other extreme. About six weeks lapse from a livebirth to first ovulation in non-breastfeeding women (Gray et al. 1987; Jones 1989). Aside from these two extremes, little is known about the distribution of times from pregnancy loss until the return of fecundity.

The second time added by a pregnancy loss is a new fecund waiting time until the

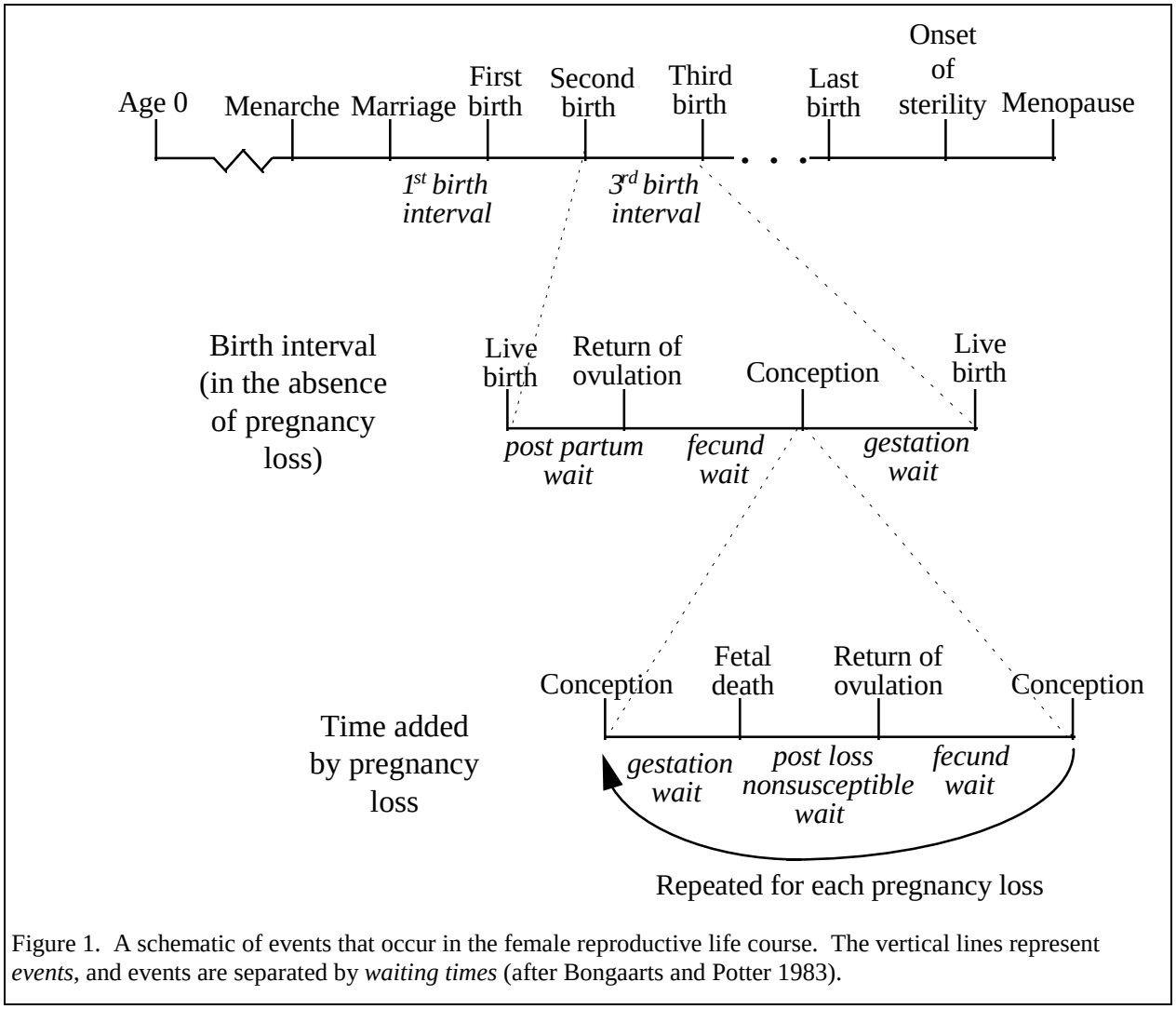

Figure 1. A schematic of events that occur in the female reproductive life course. The vertical lines represent *events*, and events are separated by *waiting times* (after Bongaarts and Potter 1983).

next conception. There has been little investigation of this waiting time, but it is reasonable to suppose that it is similar to the initial waiting time to conception in the second panel. Finally, a new period of gestation follows the fecund waiting time.

Within one birth interval, a woman may become pregnant and lose the pregnancy any number of times. The total number of pregnancies lost within a single birth interval will depend on the probability of loss for each conception. If this probability is high, multiple pregnancy losses can occur within one birth interval, each time adding three new waiting times, and resulting in a substantially lengthened birth interval. On the other hand, if the probability of pregnancy loss is very low, then the additional waiting times are rarely added even once per birth interval. A mathematical treatment of the relationship between pregnancy loss, the waiting times added by pregnancy loss and the distribution of birth interval lengths is given in Wood (1994:261).

Throughout the rest of this chapter, we examine in more detail three of the components that make up birth intervals. First we examine fecundability, which determines the fecund waiting time to the next conception. Then we examine the distribution of gestational ages at which pregnancies are lost and the overall probability of pregnancy loss. As will be clear from the discussion that follows, all three components must be treated together for a complete understanding of any one component.

Fecundability

Fecundability is defined as the monthly or cycle wise probability of conception for a couple that is sexually active, not contracepting and capable of getting pregnant (Gini 1924). This probability directly determines the waiting time to next the conception. In the simplest case, if fecundability is homogenous among women and within women, then it is simply the inverse of the mean waiting time to conception (Sheps and Menken 1973).

A number of different methods have been devised for the estimating fecundability. It has been estimated from the fraction of couples conceiving in a month (Gini 1924; Henry 1972; Potter 1961; Sheps 1965; Tietze et al. 1950), waiting times to a recognized conception (Henry 1972; Jain 1969; Majumdar and Sheps 1970; Potter and Parker 1964; Sheps 1964; Sheps and Menken 1972, 1973; Strassmann and Warner 1998), and waiting times from marriage to the first birth (Gini 1924; Bongaarts 1975; Wood et al. 1994). At the most detailed level, fecundability is found as a function of daily probabilities of conception given coitus for each day near ovulation (e.g. Barrett and Marshall 1969; Weinberg et al. 1994).

A fundamental difficulty with all measures of fecundability is that early pregnancies cannot be detected by any current non-invasive technology. Thus any pregnancies that terminate before being detected lead to underestimation of fecundability. Demographers have defined fecundability in a number of ways in order to take into account this difficulty. *Total fecundability* is defined as the true monthly or cycle-wise probability of conception, *apparent fecundability* is the monthly or cycle-wise probability of conception using a particular technology to detect a pregnancy, and *effective fecundability* is the monthly or cycle-wise probability of conception that results in a livebirth.

Total fecundability cannot be measured by existing technology; yet, it is conceptually the most important measure because it completely disentangles fecundability from the effects of pregnancy loss (which is a measure of mortality). We will revisit issues of how total fecundability and pregnancy loss are confounded as well as age-specific total fecundability after we examine pregnancy loss in more detail. Both apparent and effective fecundability are measures that confound total fecundability and pregnancy loss. Effective fecundability discounts pregnancy loss altogether. Apparent fecundability is more difficult to interpret, since we must consider the technology being used for detecting pregnancies and how early pregnancies are detected by the method.

The effect of age on apparent fecundability is fundamentally important for an understanding of birthspacing. The observed pattern of age-specific apparent fecundability based on earlier data shows a rapid increase from zero in the teens to a peak in the early twenties. Thereafter fecundability declines steadily with age until reaching zero in the mid-forties (Wood 1994). It is important to keep in mind that the age-specific decline in apparent fecundability may be biased by an age-related increase in early (i.e. undetectable) pregnancy loss. The extent this bias can only be known by measuring total fecundability.

Pregnancy loss

In trying to evaluate the effect of pregnancy loss on the human life course, we run into the same difficulty that we had for fecundability. Since some pregnancies may terminate before they can be detected, empirical studies under-enumerate the true number of pregnancies and therefore the number of pregnancies that are lost. Again, the extent of this under-enumeration depends on the characteristics (particularly the sensitivity) of the methods used to diagnose pregnancy. For this reason, it will prove useful to use the modifiers *total* and *apparent* with pregnancy loss in the same sense they were used for fecundability. Total pregnancy loss refers to all pregnancy loss from conception through term, and apparent pregnancy loss refers to losses that occur after a pregnancy is diagnosed.

As with fecundability, comparisons among studies of pregnancy loss are problematic. Even so, it is helpful to examine the results of broadly similar studies, and to see the effects that the study methods have on apparent pregnancy loss.

Community surveys

The earliest large-scale population based studies of pregnancy loss were community surveys that relied on subjects' self-reports of pregnancy. The apparent probability of pregnancy loss found in these studies are in the range 12 to 15 percent per conception. Details and summaries of some of these studies can be found elsewhere (Leridon 1977; Kline et al. 1989; Boklage 1990; Wood 1994). Determining pregnancy by self-reports is not a very sensitive assay method, so that all of these community-based studies grossly underestimated the probability of total pregnancy loss. Still, when properly analyzed, these studies provide a useful picture for the risk of pregnancy loss at later gestational ages.

hCG-based studies

A number of biochemical changes take place early in pregnancy that can be used to diagnose pregnancy (reviewed in Grudzinkas and Nysenbaum 1985). To date, the only method that has been refined, validated, and used extensively for studies of pregnancy loss involves assays for the hormone human chorionic gonadotrophin (hCG) in maternal blood or urine. These hCG-based methods show a high sensitivity, and are capable of detecting pregnancies before the end of the second week after fertilization. Even so, the most sensitive assays of this type cannot detect pregnancies until about seven days after conception (Lenton 1988), and fail to detect half of all true pregnancies up to about 10-14 days after ovulation (Holman et al. 1998).[2]

Another important characteristic of a pregnancy assay is its specificity, defined as the probability that the assay will correctly diagnose a non-pregnant as not pregnant.[3] Extremely sensitive pregnancy assays tend to have lower specificity because their extreme sensitivity picks up low levels of background hCG that occur naturally in non-pregnant women (Alfthan et al. 1987; Armstrong et al. 1984; Stenman et al. 1987). Some hCG-based assays have low specificity for another reason: they cross-react with molecules that are similar to hCG, particularly lutenizing hormone (LH). High specificity is extremely important for studies of pregnancy loss, as many assays will be carried out for every early pregnancy loss detected, so that even a small false-positive rate will bias upward the probability of pregnancy loss (Weinberg et al. 1992).

The first large-scale study of apparent pregnancy loss using hCG-based pregnancy assays was that of Miller et al. (1980), who measured urinary hCG concentrations in first morning urines taken every other day over the luteal phase of 197 women (mean age 27.5 years) who were discontinuing non-hormonal contraception. The hCG assay they used showed "very little" cross-reaction to LH. Unfortunately, additional details on specificity were not provided, and they did not use a pool of non-pregnant women to test the specificity of the assay under the conditions of study. The limit of detection of the assay was 10 IU/L hCG, and their criterion for pregnancy was a concentration above 20 IU/L hCG in two successive samples or a single sample over 50 IU/L hCG. The probability of pregnancy loss was 0.427 for all pregnancies they could detect, and 0.139 for pregnancies that were detectable by standard clinical methods. These surprisingly high rates of pregnancy loss must be interpreted with some caution because of the lack of controls and the possibility of false positive diagnoses of pregnancies.

Edmonds et al. (1982) studied pregnancy loss using the same assay as was used by Miller et al. (1980). However, they paid careful attention to issues of specificity. Subjects collected first-morning urines every other day beginning with cycle day 21. A series of 18 women who had undergone a tubal ligation served as controls; their samples

[2] The sensitivity of a pregnancy assay refers to the gestational age-specific probability (from fertilization on) that the hCG assay will detect a true pregnancy. This definition of sensitivity is appropriate for qualitative assays, such as those used to diagnose a pregnancy. A different definition of sensitivity is used for quantitative assays, such as those that quantify the concentrations of hCG. An hCG assay can be used as a pregnancy assay by defining one or more criteria that must be met before the result is considered a positive indication of pregnancy.

[3] One minus the specificity is the probability of a false positive pregnancy diagnosis. Typically, the specificity of a particular assay is determined by quantifying the number of false pregnancies diagnosed in a series of women who have had tubal ligations.

were assayed to determine the maximum concentration of hCG that could be detected in non-pregnant women. From this, they arrived at an extremely conservative cutoff of 56 IU/L hCG, which provided a specificity of 99.99 percent. They also demonstrated that cross-reaction to physiological levels of LH was negligible. Eighty-two women (mean age 27 years) discontinuing non-hormonal contraception contributed 198 ovulatory cycles. Despite the very conservative cutoff for a pregnancy diagnosis, a remarkable 62 percent of pregnancies were lost and the probability of clinically recognized pregnancies ending in loss was 12 percent.

The findings in Edmonds et al. (1982) are perplexing because about one third of the early pregnancy losses were diagnosed on day six or seven after (estimated) ovulation, and half of the early losses were diagnosed before day nine. But the relatively low sensitivity of their assay and the extremely conservative hCG cutoff they used, should have made such early detection of pregnancy unlikely. Lenton et al. (1988) showed that only five percent of spontaneous conception cycles produce hCG in concentrations exceeding 5 IU/L by day eight and 16 percent by day nine; likewise, studies by O'Connor et al. (1994) and Wilcox et al. (1985, 1988) suggest that hCG concentrations rarely exceed 50 IU/L before about the first missed menses. Wilcox et al. (1985) further examined this issue by comparing two highly sensitive and specific assays, including the SB6 antibody-based assay used by Edmonds et al. (1982). Several possible difficulties were found for the SB6 assay, including some cross-reaction with LH. One subject showed a consistent nonspecific immunoreactivity by the SB6 assay that was not found with the other assay. In this way, estimates of pregnancy loss in the Edmonds et al. (1982) study may have been biased by one or more difficulties with their assay.

Wilcox et al. (1988) studied pregnancy loss in 221 women (mean age was 29 years; 707 cycles) discontinuing contraception. A control group of 31 women who had undergone tubal ligation provided samples to develop a pregnancy criterion of 0.035 ng/ml (≈0.45 IU/L) hCG for three days. The hCG assay used a polyclonal antibody (R525) that was highly sensitive and specific (Wilcox et al. 1985). This study measured a probability of apparent pregnancy loss of 0.32, and the probability of pregnancy loss in clinically recognized pregnancies of 0.22.

Hakim et al. (1995) studied infertility and early pregnancy loss in 148 women (mean age about 32 years; 679 menstrual cycles) who worked in a semiconductor manufacturing plant. About 60 percent of the subjects reported no past or present fertility problems. They used a highly sensitive and specific monoclonal antibody-based hCG assay. The overall probability of pregnancy loss for women without fertility problems was 0.38, and the probability of pregnancy loss following a clinically recognized pregnancy was 0.21.

The hCG-based studies all provide broadly consistent estimates for the probability of *clinically* recognized pregnancy loss even though the more sensitive assay methods yielded loss rates from 0.32 to over 0.60. The large range reflects, in part, methodological differences in assays characteristics, criteria for pregnancy diagnosis, and the sampling methods used.

Anatomical studies

Hertig et al. (1956, 1959) studied early pregnancy loss by direct microscopic examinations of conceptuses. In this remarkable study, conducted from 1938 to 1954, uteri and oviducts were surgically removed from 211 women of proven fertility. Prior to surgery, the women attempted to get pregnant. One hundred and seven cases were deemed optimal for finding an early conceptus, based on ovarian signs of a recent ovulation and removal of the uterus between ovulation and the next menses. The oviducts and uteri were carefully flushed and 34 conceptuses of known gestational age were found, of which 10 appeared to be morphologically abnormal. Four of eight conceptuses recovered prior to implantation were abnormal. Of the remaining 26 conceptuses, six were abnormal. James (1970) reviewed the results of Hertig et al. (1959) and another small anatomical study, and the results of the community-based study of French and Bierman (1962). By estimating the proportion of fertilized ova that were missed in the Hertig study, he estimated a probability of total pregnancy loss of 0.49.

Age-specific pregnancy loss

Biomedical and demographic research suggests that the risk of pregnancy loss varies considerably among women within a population. An important source of this variation appears to be maternal age. The pattern that has emerging from a number of studies suggests the risk of pregnancy loss changes with age according to a U-shaped distribution. The risk of pregnancy loss declines in the years immediately following menarche, the risk is lowest around age 20, and then increases regularly with age thereafter.

Wood and Weinstein (1988) compiled results from nine studies examining the effects of age on risk of pregnancy loss. The distribution from each study was re-scaled to a common rate of 150 pregnancy losses for 1000 conceptions to account for differences among studies in methods of pregnancy determination. Apparent pregnancy loss showed a steady rise with age, increasing from a probability of 0.15 at age 20 to a peak of 0.40 toward the end of the reproductive span. From the hCG-based studies discussed above, we can conclude that the true overall rate of pregnancy loss is likely to be substantially higher at each maternal age; it is the overall shape of the curve that is of interest.

Several authors have suggested that the increased risk of pregnancy loss by maternal age or gravidity is, to some extent, a statistical artifact (Wilcox and Gladen 1982; Santow and Bracher 1989; Casterline 1989; Resseguie 1974; Leridon 1976). A bias toward higher risk of loss at older ages results from examining risk of pregnancy loss in non-natural fertility populations. If there is heterogeneity in risk of pregnancy loss among women in the population, then the group of women still attempting to reproduce at older ages may increasingly be made up of those at higher risk of pregnancy loss. In other words, in studies of pregnancy loss in contracepting populations, older subjects are those women who have not yet met their family size goals; perhaps because they are at higher risk of pregnancy loss. This selectivity hypothesis has received some empirical support (e.g. Santow and Bracher 1989); but, as Wood (1994) points out, the same elevation in

risk of loss is found in studies among natural fertility populations such as the Amish (Resseguie 1974) and rural Indian women (Potter et al. 1965).[4]

Bishop's theory of pregnancy loss

Beginning in the early 1960s, the first cytogenetic studies of spontaneous abortions were undertaken. These studies uncovered the role of lethal trisomies (Edwards et al. 1960; Patau et al. 1960), and triploidies (Penrose and Delhanty 1961; Delhanty et al. 1961) in pregnancy loss. These case studies were soon followed by larger cytogenetic studies of aborted material (Carr 1963; Clendenin and Benirschke 1963; Thiede 1969).

Marcus Bishop (1964) summarized the cytogenetic studies of human abortuses and his own work on the cytogenetics of bull sperm, and put together a theory of pregnancy loss. Bishop proposed that (1) the majority of pregnancy losses resulted from chromosomal abnormalities, (2) chromosomal abnormalities would increase with the age of parents[5], and (3) many unobserved losses would occur during the earliest parts of the pregnancy. Since Bishop's theory was first formulated, a number of lines of research have substantiated the basic elements. In particular, numerous cytogenetic studies of spontaneous abortions (reviewed in Thiede 1969; Boué et al. 1985; Warburton 1987; and Jacobs 1991) confirmed the prediction that chromosomal abnormalities are the single most common cause of human pregnancy death in conceptuses that survive long enough for the pregnancy to be recognized.

Risk of pregnancy loss may vary among women for reasons other than the increase in chromosomal errors associated with maternal age. These factors include environmental chemicals (Pernoll 1986; Brent and Beckman 1994), endocrine factors (Maxson 1986; Coulam and Stern 1994), implantation factors (McIntyre and Faulk 1986; Hunt and Roby 1994), uterine and other maternal defects (Patton 1994; Crenshaw 1986; Rock and Murphy 1986), maternal infection (Sever 1980; Byrn and Gibson 1986; Benirschke and Robb 1987), and immunological causes (Branch 1987; del Junco 1986; Silver and Branch 1994). Although these non-chromosomal causes may be important in a medical context, they share the common characteristics that each cause is individually rare.

Probability of Pregnancy Loss Across Gestation

Ideally, we want to know the risk of pregnancy loss at each gestational age. The gestational-age specific risk of pregnancy loss defines both the ages when pregnancies are lost as well as and the overall probability of pregnancy loss. Kline et al. (1989) summarized the data of the Hertig et al. (1959), Wilcox et al. (1988) and French and Bierman (1962) to arrive at an aggregate distribution for the risk of pregnancy loss across gestation that shows the risk highest immediately after fertilization and declining at all

[4] The apparent increase in risk of fetal loss at the youngest ages may result from a bias toward earlier initiation of sexual relations in women who experience menarche at younger ages (Wood 1994).

[5] Discussions of age-related changes in the risk of pregnancy loss tend to focus on maternal age rather than paternal age. Several analyses support the claim that it is primarily maternal age, not paternal age, that is most important for pregnancy loss (Hassold et al, 1980; Hatch 1983; Antonarakis et al 1991). Even so, parental ages tend to be highly correlated, so that statistical models will have difficulty teasing apart maternal and paternal age effects.

later gestational ages. Wood (1989, 1994) and Boklage (1990) took another approach to this question. They independently developed a parametric model of pregnancy loss, which captures much of the underlying theory of Bishop's model. Under the Wood-Boklage model pregnancies fall into one of two risk groups—a chromosomally abnormal group for which risk of pregnancy loss is high, and a chromosomally normal group for which risk of pregnancy loss is low. The hazard for each risk group is considered constant across gestation, corresponding to a negative exponential distribution of deaths in each subgroup. A third parameter of the model is the initial fraction of conceptuses in the high risk group.

Results from previous studies were analyzed by Wood (1989, 1994) and Boklage (1990). The parametric and etiologic nature of the model gave them the means to extrapolate the risk of pregnancy loss back to conception and thus to estimate the probability of total pregnancy loss. Wood reanalyzed the French and Bierman community survey data, and found the proportion of conceptuses in the abnormal group was 29 percent; the abnormal subgroup had a hazard of loss of 0.169 and the normal group had a hazard of 0.001. Mathematically, these estimates imply a probability of total pregnancy loss of 0.30, of which eight percent constitute those that die before clinical detection. In the high-risk group, 99.8 percent of the conceptuses perished before birth, and 3.4 percent of the low-risk group died before birth.

Boklage (1990) used results from five hCG-based studies of natural conceptions, adjusted for each study to a common probability of 0.287 at clinical detection, and then estimated the parameters of the model. The estimated fraction of abnormal conceptuses was 73 percent. The hazard for the abnormal subgroup group was 0.155, and the hazard for the normal subgroup was 0.00042. The estimates give a probability of total pregnancy loss of 0.733. The chromosomally abnormal subgroup constituted almost all of the pregnancy losses; only about 1.1 percent of the normal conceptuses were expected to be lost.

Wood's and Boklage's estimates primarily differ in the initial proportion of abnormal conceptuses. The subgroup hazards were remarkably similar, despite the very different regimes of pregnancy detection. Wood's original estimates are almost certain to have underestimated the fraction of abnormal conceptuses because the French and Bierman (1962) data used in the analysis were based on self-reports of pregnancy loss, implying that pregnancies had to survive to fairly late gestational ages to be ascertained.

Measuring total fecundability and total pregnancy loss

As should be clear from the preceding discussion, most previous work has treated pregnancy loss alone or fecundability alone. The result is that *apparent* fecundability and pregnancy loss have been estimated rather than *total* fecundability and pregnancy loss. In this section, we develop an approach for estimating both quantities together. First we examine in detail the way in which pregnancy loss and fecundability are confounded. Then we extend the Wood-Boklage model and use it as the basis of a new model to estimate total fecundability and total fetal loss.

Suppose we were to conduct a study using a pregnancy assay with perfect sensitivity. Some number of women would be followed prospectively and a test for

pregnancy made within each menstrual cycle. The results of this study might look like Figure 2 (top panel), in which some number of menstrual cycles are observed along the *y*-axis. Cycles that result in a pregnancy are followed to term along the *x*-axis. The horizontal line indicates the number of cycles in which fertilization occurred, and the dashed curve represents the numbers of ongoing pregnancies that survive to each gestational age. After all pregnancies have terminated in this study, each menstrual cycle can be classified as a non-conception cycle, a cycle that ended in the loss of the pregnancy, or a cycle that resulted in a livebirth. We could then directly compute total fecundability as described in the figure caption.

Since we cannot detect pregnancies at fertilization, a more realistic portrayal for this fictitious study is shown in the lower panel of Figure 2. The vertical line labeled "detection" represents the imperfect sensitivity of the pregnancy assay. The assay cannot detect any pregnancy before this point and it detects all pregnancies that survive beyond this point. Now each menstrual cycle must be classified in one of three ways: cycles in which a pregnancy was not detected, cycles in which a detected pregnancy is lost, and cycles that end in a livebirth. The incomplete sensitivity means that we do not know the proper denominator to compute total fecundability and we do not know the proper numerator or denominator to compute the probability of total pregnancy loss.

Figure 2 illustrates why direct measurement of total fecundability and pregnancy loss is impossible when the earliest pregnancies cannot be detected; but it also suggests a way to get around the difficulty. Suppose we had a parametric model for the gestational age-specific risk of pregnancy loss. We could use the observations of pregnancy loss taken from the point of detection forward to estimate the entire distribution of pregnancy loss. The resulting distribution could be used to compute total pregnancy loss, which, in turn, provides a basis for estimating total fecundability. This procedure involves projecting the distribution of pregnancy loss back to the start of the pregnancy, so that the model for risk of pregnancy loss needs to be an accurate reflection of the most important biological mechanisms involved in pregnancy loss.

The Wood-Boklage model is a suitable model for this purpose. The model captures the most important components of pregnancy loss as envisioned by Bishop (1964). It is parameterized by defining h_h as the hazard for the abnormal (high-risk) subgroup and h_l as the hazard for the normal (low-risk) subgroup. Both parameters are constant across gestation. The fraction of abnormal conceptuses surviving to gestational age t is $\exp(-h_h t)$. Likewise, the fraction of normal conceptuses surviving to t is $\exp(-h_l t)$. At fertilization, a certain fraction of conceptuses are chromosomally abnormal; the fraction is denoted p_h. This percentage declines over the course of gestation because abnormal conceptuses are lost at a greater rate.[6]

[6] The overall fraction of surviving conceptuses at gestational age t is $S(t) = p_h\exp(-h_h t) + (1 - p_h)\exp(-h_l t)$. The proportion of abnormal conceptuses at gestational age t is $p(t) = p_h\exp(-h_h t)/S(t)$. The hazard for the combined subgroups at gestational age t is $h(t) = p(t)h_h + [1-p(t)]h_l$. We model covariates, such as maternal age, as affecting h_h and h_l using a proportional hazard specification. For the p_h parameter, a logistic specification is used to model the effect of covariates.

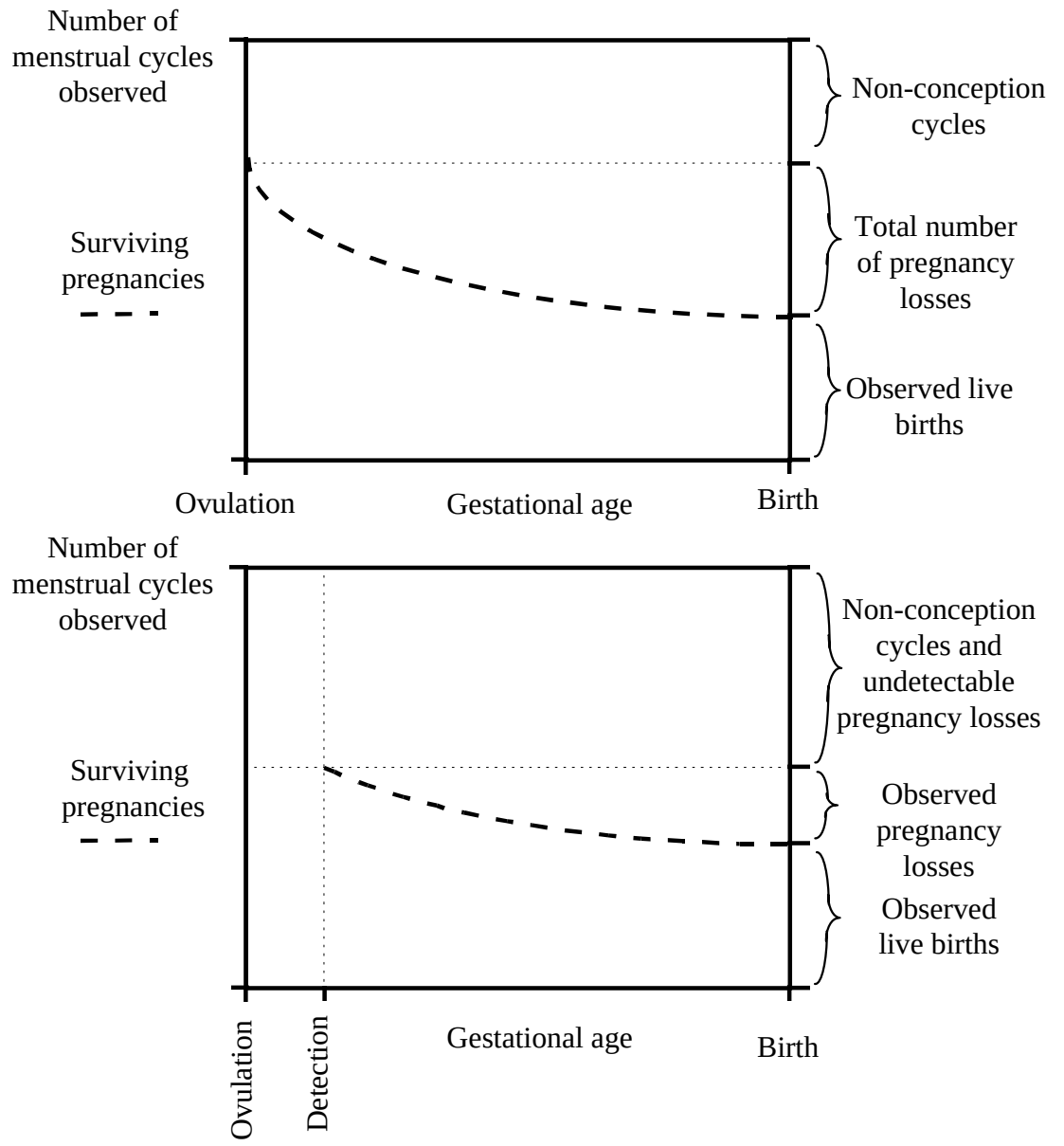

Figure 2. The way in which total pregnancy loss and total fecundability are confounded by incomplete sensitivity of pregnancy assays. The *y* axis represents some number of menstrual cycles under study, and the *x* axis is time from ovulation to birth. The upper panel shows classification of each cycle as if exact information were known. Fecundability is computed as (pregnancy losses + births)/(number of menstrual cycles), and the probability of pregnancy loss is computed as (pregnancy losses)/(pregnancy losses + births). The bottom panel shows what happens when pregnancy detection cannot occur until sometime after fertilization. The mean gestational age at which the assay can detect a pregnancy is labeled "detection". Now, the earliest pregnancy losses and the non-conception cycles cannot be differentiated. The proper numerator for fecundability is not known, and the proper numerator and denominator for estimating the total probability of pregnancy loss are not known (Holman 1996).

The Wood-Boklage model was used as the basis for a new model to estimate both age-specific total pregnancy loss and age-specific total fecundability. The data required

to estimate parameters of the model are a series of menstrual cycles along with results of pregnancy assays within each cycle. The mathematical details of the model are given elsewhere (Holman 1996), and only an overview is given here. The model incorporates the effects of both assay sensitivity and assay specificity, incorporates interval-censored and right-censored observations, and statistically estimates a non-susceptible fraction of women (i.e. those who are not at risk of getting pregnant). Controlling for the non-susceptible fraction, means that a fecundability of one will be estimated for at least one age.

The observations we used to test the model are twice weekly urine samples assayed for the presence of hCG one or more times within each ovarian cycle (Holman et al. 1998). The start of each "cycle" was taken as the estimated day of ovulation. Each cycle ended when one of three events occurred: the next menses (which includes both non-conception cycles as well undetected pregnancy losses), a pregnancy terminated, or a livebirth occurred. From observations of this type, maximum likelihood estimates were found for total fecundability (ρ_0), total pregnancy loss (p_h, h_h, and h_l), the gestational-age-specific sensitivity of the pregnancy assay, and maternal age effects on fecundability and pregnancy loss. Assay specificity (0.94) was a constant in the model.

The underlying logic of the method is seen in Figure 3. Events are occurring probabilistically from one pregnancy assay to the next within a single cycle according to the branches and branch weights of this tree. All we can observe are the positive or negative assay results shown at the branch tips. At ovulation (time t_0), a fraction of women will be pregnant with probability ρ_0 (which is the estimate of total fecundability). For women who are not pregnant (probability $1-\rho_0$), the left branch of the tree is traversed. A pregnancy assay given at the first observation after ovulation (time t_1) will give a true negative diagnosis with specificity q, and a false positive diagnosis with probability $(1-q)$. For the women who are pregnant, fraction $1-P_1$ will experience a pregnancy loss in the interval $[t_0, t_1]$; P_k arises directly from the Wood-Boklage model as $P_k = S(t_k)/S(t_{k-1})$, and incorporates parameters p, h_h, and h_l and covariate parameters. Again specificity q probabilistically changes the outcome of the pregnancy assays. For women who do not experience pregnancy losses (with probability P_1), some fraction of their pregnancies will be detected with probability equal to sensitivity D_1. Likewise, fraction $1-D_1$ pregnancies will not be detected; specificity q probabilistically can then change the result.

The tree yields four routes to a positive assay result, and three routes to a negative result for the first pregnancy assay at time t_1. For all women who have positive results, we can now compute ρ_1, the probability that they are truly pregnant at time t_1, as the sum of the two "pregnant" branches that yield positive results divided by the sum of all four "positive" branches, which is $\rho_1 = \rho_0 P_1[1-q(1-D_1)]/[1-q(1-\rho_0 D_1 P_1)]$. The probability that these women are not pregnant given a positive assay is $1-\rho_1$. For women who have negative assay results, the probability that they are pregnant (but the assay could not detect it) is $\rho_1 = \rho_0 P_1(1-D_1)/(1-\rho_0 D_1 P_1)$.

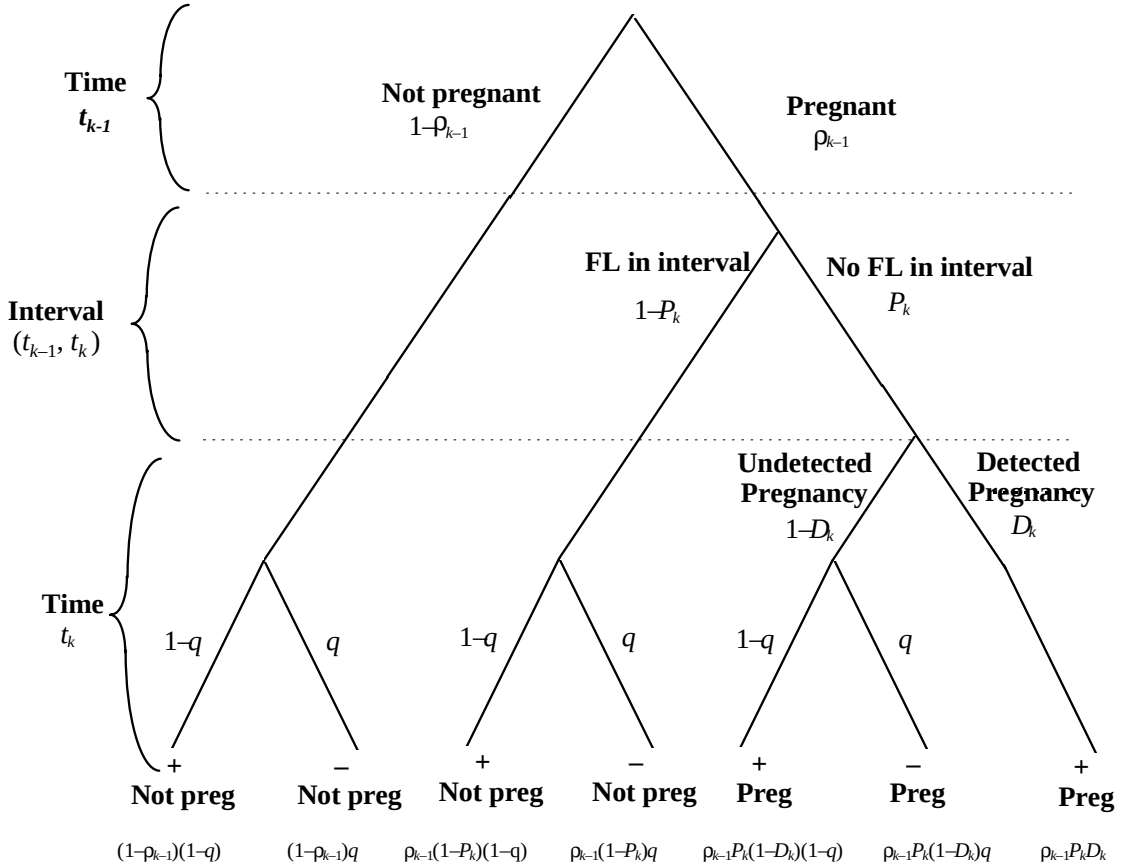

Figure 3. Probability tree showing the relationship among pregnancy assay results, characteristics of the assays, and probability of pregnancy loss across the interval (t_{k-1}, t_k); ρ_k is the probability of pregnancy at time k; P_k is the probability of no pregnancy loss occurring in the interval; D_k is the sensitivity of the assay at gestational age t_k; q is the specificity of the assay. At the terminal branches, + and – indicate whether the result of the pregnancy test is positive or negative; *Preg* and *Not preg* refer to whether the individual is pregnant or not. The probability of arriving at each of the seven outcomes is given along the bottom (Holman 1996).

The left and right branch of the tree are weighted by probability ρ_1 between the first pregnancy assay and the second pregnancy assay. The tree is probabilistically traversed again and the assay result is used to compute ρ_2 given ρ_1. The tree is traversed this way for all intervals between pregnancy assays, always computing the value of ρ_k from ρ_{k-1}.

We have given the preceding description as though values for p_h, h_h, h_l, ρ_0, D, and covariate parameters are known, whereas the goal is to estimate these parameters from observations. Because the model was specified as a series of probabilistic events, maximum likelihood methods can be used to find the parameters. Details of the model, estimation methods, statistical validations, and results are given elsewhere (Holman 1996).

Total pregnancy loss and total fecundability in Bangladeshi women

We collected data from a near-natural fertility population in rural Bangladesh in order to estimate parameters of the fecundability and fetal loss model (Holman 1996). The field study was conducted from February through December 1993 in Matlab thana, a rural sub-district of Bangladesh about 50 km southeast of Dhaka. For the first month of the study, female field workers conducted one-time interviews of almost all married women ages 18 to 48 who permanently resided with their husbands in 28 villages (N = 3,290). The 17 villages with the lowest contraceptive prevalence were selected for the nine-month prospective portion of the study. The sample included married women of all reproductive statuses, including those who were pregnant or breastfeeding at the start of the study. In this way, we did not select for subfecundity by eliminating those of proven fecundity (i.e. breastfeeding or pregnant women). Women using any form of contraception were excluded from the pool of potential participants. At any time during the prospective portion of the study, 320 subjects were enrolled. As subjects dropped out of the study or became ineligible (e.g. because of divorce), replacements were randomly selected from the pool of eligible subjects. Subjects were interviewed twice weekly about menses, pregnancy, breastfeeding, and contraception, and at the same time a urine specimen was collected. By the end of the field study, over 19,000 paired interview and urine specimens were collected from 494 subjects who participated in the study for one to nine months. Urines samples from the last one-third of all menstrual cycles were assayed for hCG to detect early pregnancies (Holman et al. 1998 provide details on the sensitivity and specificity of the pregnancy assay). The final set of observations consisted of 4,400 pregnancy assays in 1,561 menstrual cycles. A total of 329 pregnancies were followed: 81 pregnancies were ongoing at the end of the study (right censored), 151 pregnancies went to term, 84 pregnancies were biochemically detected and ended in an early pregnancy loss, 10 pregnancies were lost after the subjects were aware of the pregnancy, and 3 pregnancies ended by induced abortion.

Maternal age effects were modeled on the risk of pregnancy loss in three ways: as affecting the initial fraction of abnormal conceptuses, as changing the risk of loss for abnormal conceptuses, and as changing the risk of loss for normal conceptuses. Maternal age did not significantly affect the risk of pregnancy loss for either the normal or abnormal subgroups. The only significant effect of age, as assessed by likelihood ratio tests, was to increase the probability that a conceptus was abnormal. This result is consistent with the predictions of Bishop (1964), and supports his idea that the primary mechanism acting over the reproductive life course is an age-related increase in the proportion of chromosomally abnormal conceptuses.

The hazard of pregnancy over the course of early pregnancy is shown in Figure 4. The top panel shows the fit independent of maternal age for the parametric model and a life table model. The fits are similar, except at the earliest gestational ages, when the pregnancy assays were unable to detect all pregnancies reliably. The parametric model makes use of the observed ranges of data and fits the entire distribution. Most of the abnormal pregnancies have terminated by day 100, so that the hazard approaches that of the normal subgroup. The lower panel shows the gestational age-specific risk expected at

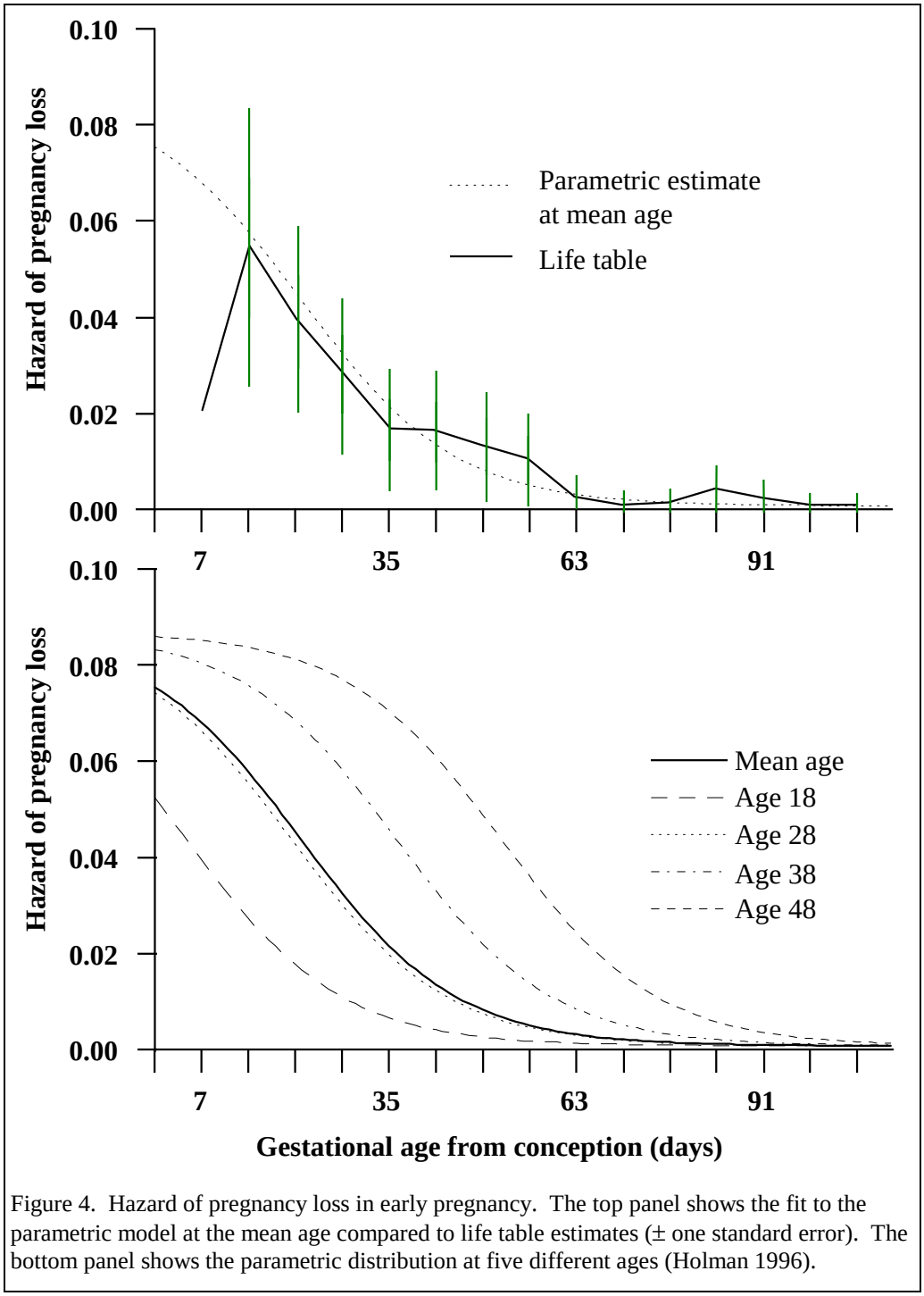

Figure 4. Hazard of pregnancy loss in early pregnancy. The top panel shows the fit to the parametric model at the mean age compared to life table estimates (± one standard error). The bottom panel shows the parametric distribution at five different ages (Holman 1996).

four different maternal ages, and at the mean age in this study.

The effect of maternal age on fecundability and pregnancy loss is shown in Figure 5. Total fecundability was constant over most of the reproductive life span. Age showed little effect from ages 20 to 36 years of age. At about 40 years of age, fecundability declined rapidly until approaching zero near age 46. The probability of pregnancy loss increases by maternal age; twenty year-old women are expected to lose about 55 percent of their pregnancies, the probability increases to 84 percent at age 30, and 96 percent at age 40. These results are similar to those of Boklage (1990), who estimated a probability of 0.73 over all ages.

Discussion

The results of this study provide a rather unexpected picture of fecundability and pregnancy loss. The age-related decline in female apparent fecundability has traditionally been interpreted as a true decline in fecundability resulting from declining coital frequency by age or marital duration (James 1981), a deteriorating uterine environment (Naeye 1983; Gosden 1985; Gostwamy et al. 1988), declining ovarian function, or an increase in the age-specific prevalence of sterility (Wilson et al 1988). The results presented here suggest that most of the age-related decline in apparent fecundability

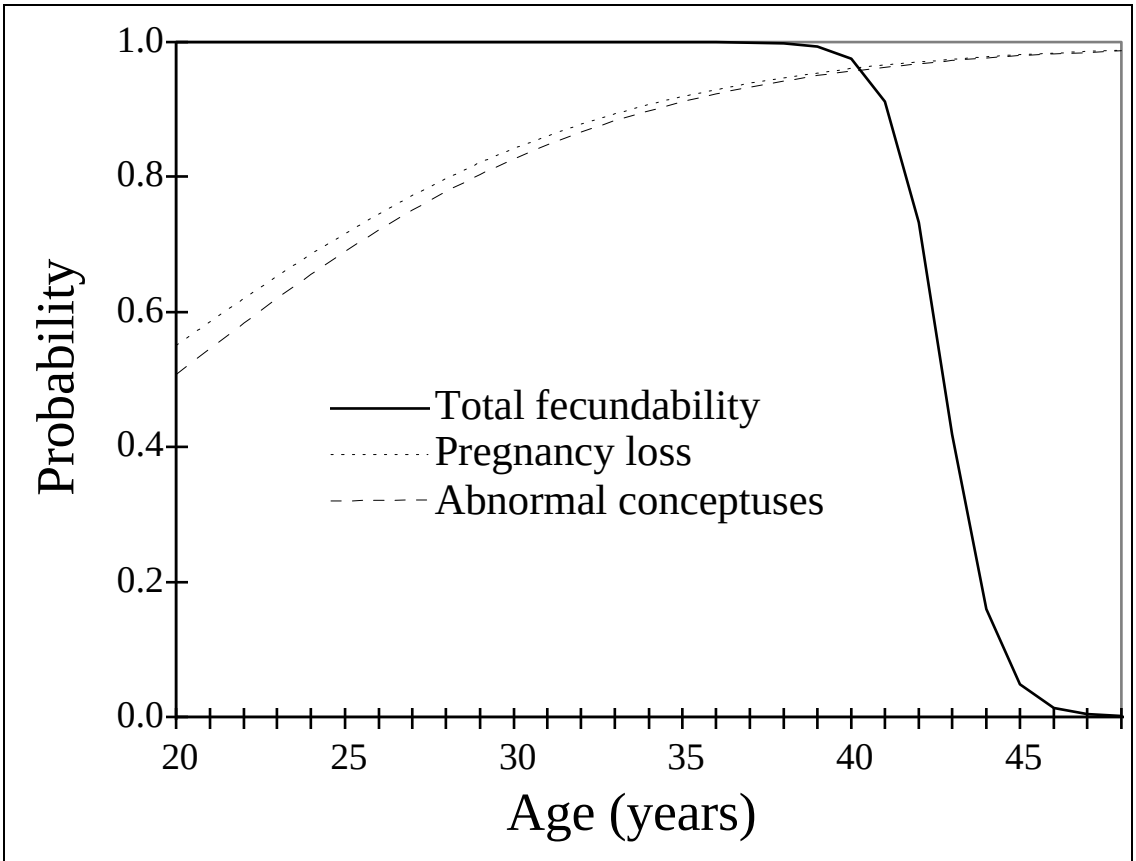

Figure 5. Estimates of maternal age-specific total fecundability and pregnancy loss in Bangladeshi women (Holman 1996).

results from an age-related increase in pregnancy loss, not from the decline in total fecundability *per se*. These other factors appear to be less important until after about age 40, when total fecundability declines sharply.

These findings provide a number of significant insights into the human pattern of reproduction. One clear implication is for our view of reproductive aging and the end of the reproductive life span. Reproductive aging appears to be a gradual process dominated primarily by pregnancy loss, followed by a rapid decline in fecundability only after age 40. By the age at which menopause is reached, fecundity is already nearly zero. In other words, menopause plays almost no role in reproductive aging and the cessation of reproduction. Because of pregnancy loss, reproductive cessation effectively occurs some time before menopause, explaining the lag of about five years between the average age of women at their last birth and the onset of menopause in natural fertility populations (Wood 1994). Hence, menopause is unlikely to affect reproductive success directly. From an evolutionary perspective, this means that menopause itself has no direct effect on fitness and therefore requires no special pleading to explain its regular occurrence in humans.[7]

This argument, of course, merely shifts the evolutionary question from "why menopause?" to "why the rapid age-related increase in the risk of pregnancy loss?" At present we have no very firm suggestions to make. Bishop (1964) suggested that, because pregnancy loss is selective with respect to chromosomal aberrations, it serves an important "editing" function in the production of viable offspring. This idea may have some merit, but it ignores the fact that high rates of pregnancy loss add substantial time to the total length of the inter-birth interval and therefore reduce overall reproductive success (Wood 1994). It has never been shown that the editing role of pregnancy loss is enough to off-set this fitness cost.

Instead of considering reproductive cessation *per se* as adaptive, we ask the question, why does the human life span extend so far beyond the age at which female fecundity approaches zero? Or, asked another way, why does female fecundity decline so early in life? This question is complex, and we can only speculate briefly here. Our first response is that this is may be a purely demographic question. Small decreases in age-specific mortality, particularly infant mortality, can dramatically increase the fraction of individuals who survive beyond age 40. It is not implausible that human cultural practices, which have likely decreased age-specific rates of mortality and the variance in mortality, are largely responsible for this pattern.

A second, and closely related, possibility is that there may be severe physiological constraints to the further evolution of the mechanism needed to extend the viability of oocytes. Alternatively, there is too little genetic variability in these systems upon which natural selection can act. As the human life span lengthened, whether through biological evolution or cultural practice, the evolution of fecundity has lagged behind. This idea

[7] This idea is supported by the otherwise puzzling findings on heritability (h^2) in age at menopause: Liqun et al. (1990) estimated an h^2 of 0.70 for age at menopause from 216 mother-daughter pairs, Peccei (1999) estimated an h^2 of 0.37 (95% CI 0.10 to 0.62) in 117 mother-daughter pairs, Snieder et al. (1998) estimated an h^2 of 0.63 (95% CI 0.53 to 0.71) from a study of 260 twin pairs, and Do et al. (2000) who estimated an h^2 of 0.51 from 426 twin pairs. Taken together, these studies suggest high heritability for age at menopause, and high heritability is usually considered evidence that a trait is not closely related to fitness (Hartl and Clark 1997).

leads to some predictions. First, it suggests that the heritability of age-specific rates of pregnancy loss resulting from chromosomal abnormalities should be very low, as any substantial genetic variability would be acted on by selection. A direct test of this idea would be difficult and invasive, but the indirect methods developed in this paper could be adapted for examining correlations among relatives. The second prediction is that these same constraints will be found in other long-lived primates, so that other species will show a similar pattern of high and increasing rates of chromosomal abnormalities at later reproductive ages.

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