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Universidad de Costa Rica

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Pinto Aguirre, Guido

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Resumption Of Postpartum Fecundability In Rural Guatemala: A Multistate Approach

Guido Pinto Aguirre¹

ABSTRACT

The purpose of this paper is to investigate and re-estimate the effects of breastfeeding patterns, women's nutritional and health status, and energy expenditure on the timing of resumption of postpartum fecundability (i.e. resumption of postpartum menses) using all the relevant information in the Instituto de Nutrición de Centroamérica y Panamá longitudinal study and a more adequate estimation procedure (hazard models). The data used in this study come from a Longitudinal Study carried out in Guatemala between 1967 and 1979. In this article we use a multi-state hazard model that recognizes different pathways and states in the process of returning to the postpartum fecundability. The model relies on the existence of five states (fully breastfeeding, partial breastfeeding, weaning, infant mortality and menses). It also includes explicitly maternal nutrition and women's energy expenditure as strategic elements of the model. The study shows that the estimated effects of breastfeeding patterns, maternal nutrition and women's work patterns (energy expenditure) on resumption of fecundability in rural Guatemala are strong and significant. The contribution of this paper is to show that application of hazard models with multiple states provides estimates that are consistent with hypotheses relating lactation patterns, maternal nutritional status and maternal external stressors to processes that accelerate (decelerate) resumption of normal menstrual cycles.

Keywords: Post-partum fecundity, breast feeding, maternal and child health

RESUMEN

El propósito de este documento es investigar y re-estimar los efectos de los patrones de lactancia, salud y estado nutricional de la mujer y consumo de energía sobre la duración del retorno de la fertilidad de postparto (es decir, retorno de la menstruación de postparto) utilizando toda la información relevante en el estudio longitudinal del Instituto de Nutrición de Centroamérica y Panamá y un procedimiento de estimación más adecuado (modelos de riesgo). Los datos utilizados provienen del Estudio Longitudinal llevado a cabo en Guatemala entre 1967 y 1979. En este artículo se utiliza un modelo de riesgo con varios estados que reconoce diferentes caminos y estados en el proceso del retorno de la fertilidad de postparto. El modelo descansa en la existencia de cinco estados (lactancia total, lactancia parcial, destete, mortalidad infantil y menstruación). También incluye de manera explícita nutrición maternal y consumo de energía de la mujer como elementos estratégicos del modelo. El estudio encontró que los efectos de los patrones de lactancia, nutrición de la madre y patrones de trabajo de la mujer (consumo de energía) sobre la fertilidad en las áreas rurales de Guatemala son fuertes y significativos. La contribución de este artículo es mostrar que la aplicación de los modelos de riesgo con múltiples estados proporciona estimados que son consistentes con hipótesis que relacionan patrones de lactancia, estado nutricional maternal y estresores maternos externos a procesos que aceleran (desaceleran) el retorno de ciclos menstruales normales.

Palabras Clave: Fertilidad post-parto, lactancia natural, salud materno – infantil

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¹ Profesor Carrera de Economía, Universidad Privada Boliviana, BOLIVIA. pinto@ssc.wisc.edu

1. Introduction

Over the last several years, an important number of social and demographic studies have examined the effects of breastfeeding, nutritional deprivation, and changes in energy expenditure on woman's fertility. However, most of this effort was conducted in the absence of a well-defined process and without the support provided by adequate models and consistent estimates.

The main reason for this preoccupation rests in the fact that nutritional imbalances, energetic stress, and longer durations of breastfeeding tend to increase the length of post-partum anovulatory periods and thus reduces woman's fertility. The discussion is mostly centered on the magnitude of the contraceptive effects of lactation (e.g. Chen et al. 1974; Delgado et al. 1978; Knodel 1978; van Ginneken 1978; Lunn et al. 1981; Huffman et al. 1987; Jones 1988; Rodriguez and Diaz 1993; Bracher 1992; Kennedy 1992; McNeilly and Visness 2001) but the extent to which a woman's nutritional status and strenuous activities –like over exercising– affect the reproductive cycle has been somewhat neglected (e.g. Chowdhury 1978; Bongaarts 1980; Lunn et al. 1981; Delgado et al. 1982; Gray 1983; Huffman et al. 1987; Warren and Stiehl 1999). Only a handful of studies have examined the simultaneous effect of breastfeeding and nutrition (e.g. John et al. 1987; Jones and Palloni 1990; Kurz et al. 1993; Popkin et al. 1993). But still remains unclear whether maternal nutritional status and energy stress during the postpartum period can disturb normal ovarian cycles independently of lactation, or whether they suppress postpartum fecundity indirectly through breastfeeding behavior.

An important data source to study these relations is the INCAP (Instituto de Nutrición de Centroamérica y Panamá) longitudinal study in Guatemala. Despite the richness of information collected through this study, data on fertility have not been analyzed using all the information gathered or by applying state-of-the-art statistical procedures. The purpose of this paper is to re-estimate the effects of breastfeeding, maternal nutrition, and changes in energy expenditure on the timing of resumption of menses in the INCAP data, using all the relevant information at hand and a more suitable estimation procedure and compare this estimates with others derived from previous INCAP studies. Methodologically we propose a model that explicitly recognizes pathways and states involved in the process of returning to the postpartum fecund state. The model relies on the existence of five states (fully breastfeeding, partial breastfeeding, weaning, infant mortality, and menses). It also considers maternal health, nutrition and women's work patterns (energy expenditure) as elements that determine the outcome of the process being studied.

The paper begins with a description of the relations underlying the physiological process of resuming post-partum menstruation. Although most of them remain unclear, important breakthroughs during the last two decades have identified the main mechanisms through which breastfeeding, nutritional imbalances, and energetic stress produce variability in the length of post-partum anovulatory periods. The next section summarizes the results obtained in previous studies using INCAP data and other sources of information. In section four we describe the data used in this paper and define the variables considered in the analysis. Section five begins with the definition of the underlying model, followed by the analysis of the main results. Finally, we provide a summary of the main results and some conclusion on the contribution of the paper.

2. The determinants of postpartum amenorrhea

The timing of resuming normal menstrual cycles in postpartum women depends on four intermediate conditions and random factors. The effects of socioeconomic characteristic are expected to operate through one of these intermediate factors (Jones 1989; Jones and Palloni 1990; Wood 1994; Pinto et al. 1998). Two of these intermediate conditions, weaning and infant mortality, if they occur before resumption of menses, have a direct causal effect. This is because both lead to termination of the nursing episodes and, therefore, of the hormonal stimulus that child suckling has on the delay of fecund menstrual cycles in breastfeeding women. The third mechanism is related to the breastfeeding patterns prevalent among those mothers who menstruated while they were still breastfeeding. The fourth mechanism is related to maternal nutrition, health status, and energy expenditure, which are also suspected to modify the hormonal stimulus by delaying the resumption of normal menstrual cycles (Wood 1994). The timing of resuming menses is also related to individual characteristics, such as capacity to breastfeed, propensity to abort spontaneously, and other biological pathways associated with ovarian activity and the reproductive axis.

It is widely recognized that intense and frequent breastfeeding episodes inhibit ovulation and that menses resumes once suckling stimulus diminishes or is terminated. Similarly, maternal nutrition and energy expenditure are thought to be linked to menstrual disturbances. There are two possible pathways through which nutritional status may affect post-partum amenorrhea. First, a deficient nutrition may directly alter woman's hormonal systems and thus induce a delay in the resumption of normal ovulatory cycles independently of breastfeeding. During prolonged energy deficit, especially when there is reduced caloric intake, woman's body goes into a state of energy imbalance and it responds by decreasing or shutting off activities that are not essential to immediate life survival, like the reproductive axis. It has been found that when energy deficit is prolonged the woman's body shuts down the ovarian production of estrogen (Frisch 1978; Cameron 2003). Second, maternal nutritional status may have an indirect effect through breastfeeding patterns (Lunn 1985). If malnourished women produce significantly lower amounts of breastmilk, their children's suckling spells will increase in intensity, thus strengthening lactation inhibitory effects. On the other hand, if the child is ill, he/she may not be able to nurse adequately and there will be a decrease in the intensity of the suckling stimulus. Finally, an increase in energy output through excessive physical activities (like exercising or athletic training) may also lead to anovulation. There are also two possible mechanisms involved. First, energy output may directly affect woman's hormonal systems and thus induce a delay in the resumption of normal ovulatory cycles independently of breastfeeding and nutritional status. Second, energy expenditure may have an indirect effect through energy imbalance. It is thought that as women restrict caloric intake and increase rigorous physical activities fat stores are decreased, creating a state of energy imbalance. The woman's body responds by shutting down the production of hormones necessary for the normal continuation of the ovulatory cycle.

Menstrual cycles are neurotransmitter phenomena driven by hypothalamic and pituitary processes. The physiological mechanism underlying this neurohormonal process originates in the hypothalamus, which is located in the basal region of the brain and is connected by a portal blood system to the pituitary (Griffin and Ojeda 2000).

Specialized neurons in the woman's hypothalamic nuclei produce the neurotransmitter *gonadotropin-releasing hormone* (GnRH), which is released in a regular and episodic fashion, and this, in turn, triggers the pulsatile release of *luteinizing hormone* (LH) and *follicle stimulating hormone* (FSH) from the pituitary. This biological mechanism is also known as the *hypothalamic pulse generator* (HPG). Normal pulsatile release of certain amounts of these hormones has been found to be crucial for normal ovarian activity and fecund menstrual cycles (Knobil 1980; McNeilly et al. 1985; Glasier and McNeilly 1990; McNeilly et al. 1994).

Additional research has also shown that normal patterns of GnRH and LH release can be severely disrupted not only by lactation but also by forms of external stress, such as energy restrictions (chronic under-nourishment, etc.) and eating disorders, increased energy expenditure (heavy physical activities, etc.), and psychosocial stress (Warren 1980; Kaiserauer et al. 1989; Loucks 1990; Genazzani 1991; Cameron 2003). However, the exact neurotransmitter signal that interrupts the pulsatile release of GnRH and thus LH during these activities has not been fully elucidated. This mechanism represents a direct link between the external environment that produce various forms of stress (i.e., stressors) and the internal regulation of the reproductive axis (Jones and Palloni 1994; Cameron 2003).

The underlying biological mechanism through which these various forms of stress suppress fertility and the regular activity of the reproductive axis have some common pathways but there are also specific mechanism associated to each type of stress. It is well established among breastfeeding women --during the postpartum period-- that the suckling stimulus is the primary signal that disrupts the normal pattern of GnRH activity. It seems that the disruption of the HPG neurons is the pathway that alters GnRH and LH release, and thus amenorrhea and fertility (Tay 1992; McNeilly et al. 1994; McNeilly 2001).

Amenorrhea has also been found to be related to weight loss and low body fat, caused by strenuous physical activities --like routine exercise--, eating disorders and dieting, and emotional stress, or a combination of all these factors. In fact, when energy deficit is prolonged woman's body shuts down the ovarian production of progesterone, which in turn inhibits the release of GnRH and thus LH. Recent research has observed that women with low caloric intake have shown high levels of *cortisol*, low levels of LH and *estradiol* (E2), and blunted responses to GnRH, which in turn disrupted normal ovarian cycles. Additionally, it has been found that thyroid function tests were abnormal, showing low total and free *thyroxine* (T4), total and free *triiodothyronine* (T3), and low or normal levels of basal TSH, which inhibits the release of GnRH. Similar results were observed among amenorrheic women that experienced simple weight loss and were not suffering from serious and chronic undernourishment (Yen 1998; Laughlin et al. 1998; Warren and Stiehl 1999; Berga et al. 2001).

Over-exercising and strenuous activities have also been linked to menstrual disturbances, like shortened luteal phase. Among athletic women, it has been observed that baseline LH, LH pulse frequency, *prolactin* (PRL), and E2 tend to be lower. In the same token, elevated *beta-endorphin* levels were found in women with exercise-induced amenorrhea, which may alter the pulsatile release of GnRH. However, the mechanism throughout *beta-endorphins* affect negatively fertility is not fully understood yet. It possible that strenuous activities lead to increased *endorphin* levels, which in turn

operate on central nervous pathways that conduce to inhibition of reproductive function. High levels of cortisol and *insulin-like growth factor binding protein 1* (IGFBP-1) have been found in women with excessive athletic training suffering from amenorrhea. Increases in cortisol levels may result from activation of central stress pathways, which may modulate the peripheral actions of insulin-like growth factor-1, and also may constrain the metabolic process that controls ovulation and amenorrhea (Kaiserauer et al. 1989; Yen 1998; Sanborn et al. 2000; Berga et al. 2001).

Finally, chronic stress conditions --like the one produced by illness-- may also lead to anovulation and amenorrhea. Women living under stressful situations have shown altered patterns of cortisol secretion and opioid "tone." The factors involved in mediating stress include *corticotropin-releasing factor* (CRF), *adrenocorticotropin hormone* (ACTH), and cortisol as well as neurotransmitters like *serotonin*, *norepinephrine*, *beta-endorphin*, *vasopressin*, *oxytocin*, and *angiotensin II*. It is also well known that in stressful situations, the adrenergic and serotonergic systems are activated. It is thought that stress increases CRF levels which in turn inhibits GnHR neurons preventing LH and FSH release. The result is decreased GnRH release and diminished pulsatility that leads to inhibition of gonadotropin release and, thus, to anovulation and amenorrhea (Gallinelli et al. 2000; Meczekalski et al. 2000).

3. Previous studies

The existing body of literature suggests that post-partum amenorrhea is strongly and consistently related to breastfeeding, even after controlling for potentially confounding factors, but its association with nutrition and energy expenditure is rather tenuous. The studies are quite heterogeneous. Some of these studies are based on aggregate cross-sectional demographic surveys (e.g. Tyson and Perez 1978; Bongaarts and Potter 1983; Guz and Hobcraft 1991). Other studies rely on clinical observations (e.g. Howie and McNeilly 1982; Rodriguez and Diaz 1993; Diaz 1989). Only a small group of studies including the Gambian project, INCAP in Guatemala, MATLAB in Bangladesh, NGAGLIK in Indonesia, and CEBU project in the Philippines rely on longitudinal protocols (e.g. Delgado et al. 1978; Lunn et al. 1980, 1981; Bracher and Santow 1982; Huffman et al. 1987; Santow 1987; Jones 1990; Jones and Palloni 1990; Kurz et al. 1993; Popkin et al. 1993; Pinto et al. 1998). Although in all these studies the goal is to investigate the role played by either woman's nutritional status or woman's breastfeeding behavior on the resumption of menses, few of them have examined the joint effects of breastfeeding patterns (duration, frequency, intensity, and type of breastfeeding) and nutritional status on the risk of resuming fertility, while simultaneously controlling for other intermediate factors such as energy expenditure, health status, infant mortality and characteristics such as age, parity, and education (John et al. 1987; Jones and Palloni 1990; Kurz et al. 1993; Popkin et al. 1993; Pinto et al. 1998).

The most important conclusion that can be drawn from these studies is that lactation increases the duration of postpartum amenorrhea and that long-term breastfeeding is statistically associated with long periods of postpartum amenorrhea, ovarian inactivity, and reduced fertility (e.g. Knodel 1978; Van Ginneken 1978). In the absence of breastfeeding, the average amenorrheic period may last between one and three months (Jones 1989); but when nursing is initiated just after childbirth, the

duration of amenorrhea increases systematically with the duration of breastfeeding at progressively slower rates (Boongarts and Potter 1983; Santow 1987; Jones 1988). However, long durations of breastfeeding do not always result in longer periods of amenorrhea, nor do they provide complete contraceptive protection (Potter et al. 1965; Jain et al. 1970; Van Ginneken 1977). Supplementation, by reducing suckling intensity and curtailing high-frequency episodes of lactation, seems to be the most important factor that explains why prolonged breastfeeding does not always extend the average time of amenorrhea beyond 18 or 20 months (e.g. Delgado et al. 1982; Howie and McNeilly 1982; Trussell et al. 1989; Jones 1990). It is relatively well established that the relationship between breastfeeding and postpartum amenorrhea depends heavily on the effectiveness of the nursing stimulus (Tyson and Perez 1978). When breastfeeding is prolonged, frequent, and intensive, the average postpartum amenorrhea may last from one to two years (Cantrelle and Ferry 1979; Wood et al. 1985; Huffman et al. 1987; Jones 1988, 1990; Rodriguez and Diaz 1993; Zohoori and Popkin 1996).

The idea that nutrition, energy expenditure, and health affect women's fertility is also present in the demographic and biological literature but is supported by weaker and less convincing evidence than that found for breastfeeding (e.g. Frisch 1975, 78; Stein and Susser 1975; Bongaarts and Delgado 1979; Warren 1980; Bullen et al. 1985; Carpenter 1994; Cameron 2003). The notion that poor maternal nutritional status may decrease a woman's reproductive capacity is based on three empirical evidences. First, long durations of postpartum amenorrhea are more often found in populations where women are undernourished than in populations where women are better nourished (Chavez and Martinez 1973; Carael 1978; Warren 1980). Second, menstrual cycles cease during times of famine and starvation (Keys et al. 1950; Stein and Susser 1975; Chowdhury 1978). Third, menstruation is also delayed when energetic stress is present in the form of anorexia nervosa, vigorous exercise, or severe depression (Warren 1980; Pirke et al. 1985; Pirke et al. 1989; Warren and Stiehl 1999; Cameron 2003). However, there is uncertainty about the effects of nutrition on the female's reproductive system in less extreme situations as, for example, when malnutrition is chronic or varies from mild to moderate rather than being acute (Delgado et al. 1978; Huffman et al. 1978, 1980, 1987; Prentice 1980; Bongaarts 1983).

Some authors have suggested that maternal nutritional status may have an important and independent effect on the risk of resuming ovulation after childbirth (Frisch 1978; John et al. 1987). But the majority suggests that the evidence reveals direct effects of maternal nutritional status on postpartum amenorrhea that are small and unimportant except under extreme conditions (Chowdhury 1978; Delgado et al. 1978; Huffman et al. 1978, 1987; Bongaarts and Delgado 1979; Bongaarts and Potter 1983; Jones and Palloni 1990; Popkin et al. 1993). However, this evidence also indicates that the indirect effects of malnutrition, through selected mediating factors may be more consequential (Kurz et al. 1993; Lunn et al. 1980; Lunn 1985). One of these mediating factors is the pattern of lactation itself seems. In fact, several studies have found that children born to malnourished mothers tend to suckle more frequently and intensively to obtain adequate amounts of breastmilk, thus increasing the inhibition of the ovulatory hormones, which lengthens the amenorrheic interval (Salber et al. 1966; Wray 1978).

A handful of studies using INCAP data found consistent associations between breastfeeding patterns,

mother's nutritional status, and duration of post-partum amenorrhea (Delgado et al. 1978, 1980; Bongaarts and Delgado 1979; Kurz et al. 1983). While these studies are important landmarks, they share some shortcomings that undermine the robustness of their results. First, these studies have utilized modeling techniques (mostly linear) that did not take advantage of the time-varying nature of the INCAP study design. Such procedures may generate inconsistent and inefficient estimates of the effects under study. Second, there is an inadequate statistical treatment of the simultaneous effect of the factors being considered. The previous INCAP studies assessed these effects in a piecemeal fashion and with a limited control for covariates, thus increasing the risk of contamination for unmeasured characteristics. Third, early studies did not make a full use of the available information on breastfeeding, maternal nutrition and other characteristics, taking advantage of their dynamic nature. Finally, the INCAP studies failed to take appropriate account of mothers whose children died before resumed menses, thus creating a selection bias problem.

In what follows we re-assess the empirical relationship between post-partum infertility on the one hand, and breastfeeding behavior, maternal nutritional status, energy expenditure, infant mortality, and health status, on the other hand. We use multi-state hazard models to incorporate time-varying effects. Methodologically we propose a model that explicitly recognizes pathways and states involved in the process of returning to the postpartum fecund state. The model relies on the existence of five states (fully breastfeeding, partial breastfeeding, weaning, infant mortality, and menses). It also considers maternal health, nutrition and women's work patterns (energy expenditure) as elements that determine the outcome of the process being studied. The model is estimated with reconstructed INCAP data, fully incorporating all the pertinent information available for the information. The model we use is well suited to retrieve information on the link between the physiology of post-partum anovulation, with its biological and social determinants to allocate the later among the intermediate pathways. A non-trivial resource that is available from this model is the ability to deal correctly with child death. As mentioned above, the practice of eliminating from the sample all mothers whose children died before resumption of menses led to selection bias and to inconsistent estimates since child's mortality risks, child nutritional status, and maternal nutritional status are correlated with each other.

4. Description of the data

The data used in this paper come from a Longitudinal Study in Guatemala carried out by INCAP on a chronically malnourished population (Read and Habicht 1993). It was designed as a prospective intervention of the physical and mental development of infants in four rural villages. A sample of 755 women was followed longitudinally by regular visits for nearly eight years, between 1969 and 1977. Women entered the study on the basis of their reproductive history; the main condition was that they had at least one child less than seven years old. At regular intervals throughout their pregnancy and postpartum period, mothers provided information about the status of their children and their own conditions. For the purpose of this reassessment, we retrieved data for all women who had a delivery between 1 January 1969 and 28 February 1977, and who were followed-up until the latter date (when the survey officially ended). In all, we selected 608 women and 1,430 birth intervals. To handle missing information for some of the variables, such as the nursing episodes per day and mother's

nutritional status, we defined categorical variables that include categories to capture cases with missing values. This enables us to use 1,417 birth intervals, nearly the full sample. According to Table 1, about 26 percent of the cases can be considered as censored information on the duration of postpartum amenorrhea.

5. Modelling strategy

The data analyzed in this paper are characterized by the presence of right-censored observations. This means that there are women who do not have ending times for the duration of amenorrhea, breastfeeding, partial breastfeeding, and infant death, either because they were not present during the survey (lost on follow-up) or because they had not experienced the event in question when the survey ended (termination of follow-up).

The reproductive history of a woman is considered as collection of random points over time (i.e., a stochastic process) defined by a sequence of events such as births, infant deaths, nursing episodes, weaning, menses, illness spells, malnutrition episodes, and supplemental food intakes that occur randomly over time. To analyze the process involved we use a state-space model with five states. The first is the origin state represented by amenorrhea following the birth of a child and the final is the destination state corresponding to an absorbing state making the arrival of menstruation. That is, women are classified into **five** groups (i.e., states), according to the type of event they experienced at every particular time during the follow-up. The first state (**fully** breastfeeding) contains all women who initiated lactation after the birth of their children. The second state (**partial** breastfeeding) is made up of those women who were nursing their children and started to introduce supplemental food in their children's diet. The third state (**weaning**) contains all women who stopped breastfeeding their children before menses resumed. The fourth state (**infant death**) is made up of all women whose children died before menses resumed. Finally, the absorbing state (**menses**) contains all women who resumed menses at various times before the survey ended. The absorbing state (waiting time to menses) is defined in Annex 1. The nutritional and health status variables are treated as time-varying covariates but energy expenditure, frequency of breastfeeding, and all socio-economic variables are considered as fixed covariates.

To deal with censored information, in this study we use multi-state hazard models (Lawless 1982; Palloni and Sorensen 1990). That is, the structure of the process studied can be represented by a succession of all these states and their transitions, as can be seen in Figure 1. The transitions in this study are defined as follows: Once a woman gets into state 1 (**full** breastfeeding), she is at risk of ending in state 2 (**partial** breastfeeding), state 3 (**wean**), state 4 (**death**), or state 5 (**menses**). When a woman introduces supplements (state 2) she is at risk of moving to either state 3 (**wean**), state 4 (**death**), or state 5 (**menses**). When a woman terminates breastfeeding her child (state 3) she is at risk of ending in either state 4 (**death**) or state 5 (**menses**). Finally, women can move from state 4 (**death**) to state 5 (**menses**). The transitions from one state to another are governed by a set of **transition rates** (Palloni and Sorensen 1990), which have the following general form:

$$h_{jk}(t_0, t_j | Z) = h_{jk}^0(t_0, t_j) \exp(\beta Z)$$

Where j is the origin and k is the destination state, t_0 is the time since the process started (i.e., time since last birth), t_j is the time spent in state j , β is a vector of covariate effects, \mathbf{Z} is the vector of fixed and time-varying covariates associated with the mother and her child, and $h^0(\cdot)$ is the origin-destination hazard baseline which depends on t_j . The aim of the multi-state model is to retrieve the parameters for the distribution of waiting times to partial breastfeeding, weaning, infant death, and resumption of menses by modeling the corresponding transition risks (Kalbfleisch and Prentice 1980; Tuma and Hannan 1984; Blossfeld et al. 1989).

6. Results

In Table 2, we present estimates for a multistate model with no covariates (baseline or null model) using a Gompertz distribution for each transition. As shown in this table, all the slopes are statistically significant, except for the transition from wean to menses. From these results we can observe the direction of the changes in the hazards rates over time; for instance, the baseline hazard rates from full to partial and partial to wean tend to increase over time (positive slopes), which means that as children grow older, mother's milk becomes a less important component in their diets, since their feeding requirements change over time, since their feeding requirements change over time.

We also can see that risks for the transitions whose destinations are menses increase over time, which is driven by the progressive decrease in the levels of hormones that inhibit menses. The estimated rates show that women who experience infant deaths or wean their children move faster to the menses state when compared to all others; in fact, they have the largest estimated coefficients. Moreover, there are large differences in the risk of resuming menses for women who experience the death of their infant before menses resumed. The risks are about 65.4 [$\exp(-0.889)/\exp(-5.070)$] times larger than if the woman is fully breastfeeding, 18.4 [$\exp(-0.889)/\exp(-3.800)$] times higher than if the woman is partially breastfeeding, and about 1.1 [$\exp(-0.889)/\exp(-0.945)$] times higher than if the woman weans her child but she/he survives.

Therefore, the "null" model replicates quite well the results obtained in a two-state model, where weaning and infant deaths were treated as time dependent covariates. The relative risks of resumption of menses for those women in states 1, 2 and 3 are roughly the same as those estimated in a two-state model (Pinto et al. 1998).

After we experimented with alternative models, a parsimonious model with covariates was estimated for each transition using also a Gompertz distribution, except for the transition from wean to menses, which was assumed to follow an exponential function as seen in Table 3. Since the hazards for all transitions are estimated simultaneously, each transition can be interpreted as if it were a two-state model, after controlling for all the other risks (transitions) to which women are exposed. Thus the effects of covariates on the hazard have the same interpretation presented in a previous analysis of a two-state model (Pinto et al. 1998).

The estimates of the hazard models for all transitions are displayed in Table 3 as well as the effects

of woman's age, parity, place of residence (atole or fresco, according to supplement dietary), mother's education, type of occupation, and frequency of breastfeeding as fixed covariates while maternal nutrition, child nutrition, nursing intensity, and health measures for mother and children as time dependent covariates. Listed across this table there are 10 columns of estimates. The first column reports estimates for the transition from fully to partial breastfeeding, the second column shows estimates for the transition from fully breastfeeding to wean, and so on. After controlling for all the relevant covariates in the model, we can see that the duration dependencies in each transition remain significantly different from zero and in the proper direction. The fact that a positive duration was found in the transitions from **full** breastfeeding to **menses** and **partial** breastfeeding to **menses** means that the risk of resuming menses associated with these two breastfeeding states increases, net of all the other factors. These results support the notion of the existence of an underlying "aging" process in the inhibitory mechanism that leads to resumption of ovulation, regardless of breastfeeding status (McNeilly et al 1985). The model also reveals the existence of an important duration dependency when women transit from **partial** breastfeeding to **wean**. The "aging" effect is again relevant to this transition. The transition from **partial** breastfeeding to **menses** has particular importance, because it resembles the transition from amenorrhea to menses in the two-state model, purged of all other determinant or causal mechanisms that lead to menses (i.e. weaning and infant death).

Breastfeeding variables are also significant in determining the resumption of menses among those mothers who are partially breastfeeding. As we can see in model **partial** to **menses**, women who nursed their children on demand (12 or more times a day) have a considerable delayed in resuming menses than those who nursed between one and seven times a day on average. According to this model, the risk of resuming menses associated to those mothers who breastfed with medium and high frequency is 0.69 ($\exp(-0.37)$) and 0.41 ($\exp(-0.894)$) of the risk for mothers who breastfed with low frequency. The effect of breastfeeding intensity is also properly signed and statistically significant. Mothers who nursed their children at lower intensity of suckling have a risk of returning to menses 28 % ($\exp(0.246)$) higher than those mothers did not. This finding regarding is consistent with the claim that higher frequency of breastfeeding and higher intensity of nursing episodes are the root of the inhibitory effects of breastfeeding: suckling stimulates the neural receptors located in the breast nipples that connect directly to the hypothalamus. Children suckling send the signal that disrupt and reduce the release of GnRH and LH, thus inhibiting ovulation and the return of normal menstrual cycles. As the duration, frequency, and intensity of lactation decrease, release of GnRH and LH recovers its normal levels, pulse frequency, and amplitude; thus, menstruation and ovulation are resumed.

One of the most important findings is that women's work patterns (proxy for energy expenditure) appear to be a powerful inhibitor of ovulation. We can observe that strenuous work (agricultural and heavy manual work) reduces considerably the risk of resuming menses, which is indicated by the size of the estimate, its negative sign, and its statistical significance. In fact, the estimated effects in the transition from **partial** breastfeeding to **menses** indicate that the risk of resuming menses in women who are engaged in agricultural activities is only half ($\exp(-0.587)$) of the risk to which women who do not work outside the home (homemakers) are exposed, after controlling for breastfeeding patterns and nutritional status. Women who work in agricultural activities may be exposed to heavy

workloads and spend considerably amounts of energy in daily activities, while women working in skilled activities or as homemakers tend to spend less energy during the post-partum period. Homemakers may get help from their older children or other relatives during this period, thus being able to reduce the load of strenuous physical activities involved in cleaning, carrying water and firewood, and washing clothes (Mejia 1972). These results are consistent with those found in the Ngaglik Study in Indonesia (Jones and Palloni 1990). The similarity of results between both studies points to the fact that strenuous work activities and high-energy expenditure, similar to over-exercising, are important factors in the process of resumption of post-partum fecundity.

This finding confirms a less explored hypothesis about the existence of independent effects of energy stress conditions (like over-exercising and strenuous activities) on amenorrhea through biological mechanisms that inhibit ovulation. It is argued that various forms of physical and psychological stress may disrupt the pulse generator neurons in the hypothalamus by triggering the release of neurotransmitters like beta-endorphin, which alters the pulsatile release of GnRH and LH, required for normal menstrual cycles (Lunn et al. 1981; McNeilly et al. 1985; Rosetta 1989; Yen 1998; Sanborn et al. 2000; Berga et al. 2001).

Another important finding is related to the effects of woman's nutritional variables on resumption of post-partum menses. In Table 3, we can see the hazard model for transition from **partial** to **menses** shows that the effects are in the expected direction and attain statistical significance. First, the measure for mother's nutritional status, BMI (body mass index) has, as expected, a positive effect on resumption on menses and it is statistically significant. In fact, the risk of returning to menses for women with high BMI is about 30 per cent, ($\exp(0.260)$), larger than the risk for women with low BMI (undernourished mothers). Second, mother's clinical supplementation, although not a direct measure of her body composition, has a relatively large, positive, and significant effect on the hazard of resuming menses. In the same table we can observe that women with high caloric intake have a risk of returning to menses that is 47 per cent, ($\exp(0.383)$), higher than those women with low caloric intake. Note that these effects are observed after controlling for variables through which maternal nutrition may operate, namely suckling stimulus. Thus, this finding stands the idea that maternal nutrition only affects indirectly by altering the intensity of suckling episodes (Kurz et al. 1993). Again, the results obtained confirm the existence of a biological mechanism associated to energy restrictions, such as chronic undernourishment, that disrupts normal patterns of GnRH and LH release. Amenorrhea has found to be associated with low body fat and weight loss. It is though that when energy deficit is prolonged woman's body shuts down the ovarian production of progesterone, which in turn inhibits the release of GnRH and thus LH. Similarly, it has been observed that women with low caloric intake have shown high levels of *cortisol*, low levels of LH and *estradiol* (E2), and blunted responses to GnRH, which in turn disrupted normal ovarian cycles.

Results for child health and nutrition support the idea that children's illness and malnourishment may inhibit ovulation by decreasing the intensity of the suckling stimulus. In fact, the relative risk of resuming menses is 1.25 ($\exp(0.226)$) higher when the child is poorly nourished and 0.90 ($\exp(-0.100)$) lower when the child is in good health. However, only the first risk attains statistical significance.

The risk of moving from **full breastfeeding** to **menses** is primarily determined by mother's age, parity, education, and frequency of breastfeeding and child's health. These effects are all statistically significant. The estimates show that high parity women, young women, and women with no education tend to resume menses faster than their low parity, old, and more educated counterparts. Also, those women who nurse on demand resumed menses slower than those who nurse more infrequently, after controlling for all the other variables.

Finally, in the transitions from **wean** to **menses** and from **death** to **menses** no covariates have significant effects on the hazard of resuming menses. This result was certainly expected because wean and death are the direct causal mechanism that lead to menses; that is, once the child is weaned or the child dies, biological and physiological factors take over the process. It is important to realize that this fact also remains hidden in a two-state model (Pinto et al. 1998).

7. Summary and conclusions

The results obtained in this article are in general agreement with those found in other socio-demographic studies and are consistent with hypotheses suggesting that resumption of postpartum fecundity, and thus resumption of menses, depends on a particular hormonal balance, which in turn depends on suckling stimulus, nutritional status and energy expenditure (Huffman et al. 1987; Jones and Palloni 1990; Popkin et al. 1993). The multi-state model confirms the importance of breastfeeding and infant mortality in the process of resuming menses. In consequence, the inclusion of infant death in the model is of nontrivial significance.

A first finding confirms the importance of breastfeeding patterns (frequency and intensity) as an inhibitor of ovulation. These effects are strong, statistically significant, and result in important reductions of levels of fertility.

An important finding suggests that energetic effort and maternal nutritional status also play an important part in explaining the resumption of postpartum fecundity. The effects of maternal work -- and the implied level of energy expenditure-- on resumption of menses are significant and in the expected direction. That is, the role of women's energetic stress is a factor that reduces the risk of resuming menses. Although, the measurement of strenuous activities (pattern of work associated with occupations) is far from perfect and may be contaminated, the results suggest it has an importance not recognized before. However, this factor only operates when women are fully or partially breastfeeding.

The effects of maternal nutritional deprivation, measured by women's BMI, are also strong, significant and in the expected direction, even after controlling for breastfeeding and work patterns. However, the inhibiting effects of maternal nutritional status on menses is reinforced when the women are fully or partially breastfeeding, but not to the same extent. These differential effects could be associated with the fact that the suckling stimulus may be stronger for malnourished mothers than for well-nourished mothers (Lunn et al. 1981).

From the methodological viewpoint, the major conclusion of this study is that the multi-state model represents the process of resuming fecundity after delivery more accurately than the two-state model (Pinto et al. 1998). In the two-state model, every woman is assigned to the same risk set, no matter how different their biological propensities to resume menses are. For instance, women whose children died are more likely to resume menses than those who are fully breastfeeding. Since these facts are "invisible" in the two-state model, it treats women that have different propensities and pathways to reach the menses state equally. Instead, the multi-state modeling strategy treats them differently, accounting for aggregated or state-specific heterogeneity.

These results have important implications for fertility trends in low contraceptive societies. On the one hand, as these societies experience a modernization process, their feeding patterns are likely to be changed, from universally long breastfeeding patterns to non-universal short breastfeeding patterns. The most immediate consequence could be an increase in fertility due to a shortening of the anovulatory period. On the other hand, modernization of these societies will tend to improve, on average, women's nutritional status, which should shorten the average anovulatory period and could also increase fertility in the long run. However, the very same process will tend to increase child survival, which should lengthen the average waiting time to menses, which could have a depressing effect on fertility.

Finally, the effects estimated are so strong that even if biological mechanisms operate alone --if no voluntary changes in childbearing targets are considered-- we should appreciate important changes on the aggregate level.

8. References

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Table 1: Frequency distribution of child-woman records by socio demographic characteristics and size of the sample. Guatemala (1967-1976).

Social and demographic Characteristics	Sample	
	N	%
Women's parity: One child	250	17.6
2 or 3 children	421	29.7
4 or more	746	52.6
Women's age: 13-19 years	168	11.9
20-29 years	722	51.0
30-49 years	527	37.2
Women's education: 0 or 1 year	394	27.8
2 or more	791	55.8
Missing	232	16.4
Women's work patterns: Housewives	839	59.2
Agric. and manual workers	74	5.2
Merchants, skilled workers	264	18.6
Missing	240	16.9
Type of supplementation: Atole	765	54.0
Fresco	652	46.0
Frequency of breastfeeding: Low (1-7 times/day)	198	14.0
Medium (8-11 times/day)	345	24.3
High (12 + times/day)	215	15.2
Missing	659	46.5
Women's nutritional status: Low (bmi<20)	496	35.0
High (bmi>20)	499	35.2
Missing	422	29.8
Post-partum amenorrhea status: Censored cases	370	26.1
Failures	1047	73.9
TOTAL	1417	100.0

Source: INCAP Longitudinal Study.

Table 2: Estimated effects (*) for multistate hazard models.

Transitions	Coeff.	Slope	Est. Rate	Chi-Sq.	N
Full (1) -> Partial (2)	-1.604 (0.00)	0.023 (0.00)	0.220	9.22 (0.00)	1262
Full (1)-> Wean (3)	-5.017 (0.00)	-0.718 (0.00)	0.002	12.31 (0.00)	10
Full (1)-> Death (4)	-3.242 (0.00)	-0.7175 (0.00)	0.010	72.65 (0.00)	59
Full (1)-> Menses (5)	-5.070 (0.00)	0.130 (0.00)	0.012	25.93 (0.00)	68
Partial (2)-> Wean (3)	-4.698 (0.00)	0.101 (0.00)	0.029	142.36 (0.00)	312
Partial (2)-> Death (4)	-5.078 (0.00)	-0.102 (0.00)	0.003	6.70 (0.01)	29
Partial (2)-> Menses (5)	-3.800 (0.00)	0.084 (0.00)	0.057	185.71 (0.00)	617
Wean (3)-> Death (4)	-1.596 (0.00)	-0.172 (0.00)	0.026	16.46 (0.00)	16
Wean (3)-> Menses (5)	-0.945 (0.00)	0.007 (0.51)	0.429	0.43 (0.51)	261
Death (4)-> Menses (5)	-0.889 (0.00)	0.050 (0.01)	0.529	5.89 (0.02)	101

(*) p-values are shown in parentheses

The duration structure is defined as a Gompertz function.

Full: fully breastfeeding
 Partial: partial breastfeeding (supplement introduced)
 Wean: child weaned before menses
 Death: child died before menses
 Menses: resumption of menses

Table 3: Covariate effects (*) for multistate hazard models.

Covariates	Transitions				
	1→2	1→3	1→4	1→5	2→3
Constant	-0.173 (0.30)	-5.017 (0.00)	-3.139 (0.00)	-3.738 (0.00)	-4.504 (0.00)
Slope	0.078 (0.00)	-0.718 (0.02)	-0.742 (0.00)	0.178 (0.00)	0.102 (0.00)
BACKGROUND VARIABLES					
PARITY: One child	0.091 (0.34)			0.234 (0.48)	0.206 (0.30)
Four or more children	0.067 (0.38)			-1.086 (0.01)	0.268 (0.08)
AGE: 13-19 years	-0.016 (0.88)		0.687 (0.06)	0.589 (0.08)	0.555 (0.01)
30-49 years	0.105 (0.14)		0.856 (0.00)	0.333 (0.41)	-0.206 (0.14)
EDUCATION: 0 or 1 year	-0.040 (0.55)			-1.147 (0.00)	-0.184 (0.19)
RESIDENCE: Atole	0.429 (0.00)			0.461 (0.07)	-0.278 (0.03)
BREASTFEEDING VARIABLES					
Medium frequency (8-11 times)	0.198 (0.04)		-5.459 (0.24)	-0.333 (0.44)	-0.453 (0.02)
High frequency (12+ times)	-0.316 (0.00)		-1.818 (0.09)	-1.326 (0.03)	-0.632 (0.00)
Low intensity nursing	0.300 (0.00)				0.336 (0.11)
MOTHER'S NUTRITION					
BMI>20					
High caloric intake	0.089 (0.44)				-0.402 (0.06)
CHILD'S NUTRITION					
Poorly nourished					0.411 (0.04)
MOTHER'S HEALTH					
No morbidity	-0.331 (0.00)				
CHILD'S HEALTH					
No morbidity	-0.104 (0.24)		-2.524 (0.00)	-1.218 (0.00)	-0.03 (0.85)
ENERGY EXPENDITURE					
Agric. And manual workers	-0.222 (0.09)				
Merchants, skilled workers	-0.184 (0.02)				
Partial log L	-2691	-67	-209	-324	-1315
Chi Square	960	12	241	91	206
d.f.	22	1	8	13	19
N	1262	10	59	68	312

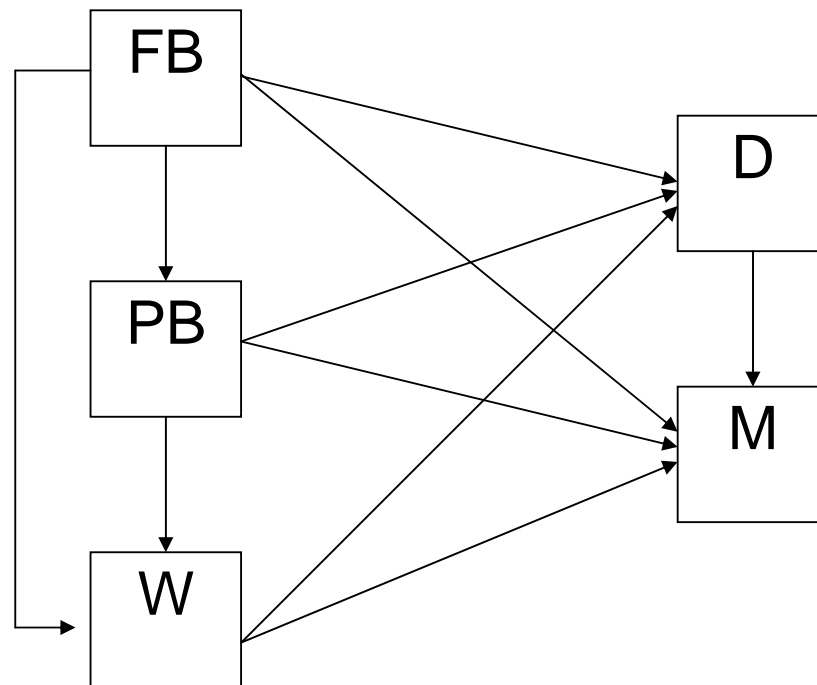
(*) p-values are shown in parentheses

Table 3: Covariate effects (*) for multistate hazard models. (continued)

Covariates	Transitions				
	2→4	2→5	3→4	3→5	4→5
Constant	-5.078 (0.00)	-3.884 (0.00)	-1.596 (0.00)	-0.773 (0.00)	-0.889 (0.00)
Slope	-0.102 (0.02)	0.122 (0.00)	-0.172 (0.00)		0.050 (0.01)
SOCIO DEMOGRAPHIC VARIABLES					
PARITY: One child		0.284 (0.03)		-0.089 (0.69)	
Four or more children		-0.252 (0.02)		0.188 (0.26)	
AGE: 13-19 years		0.411 (0.01)		0.019 (0.94)	
30-49 years		-0.107 (0.29)		-0.257 (0.07)	
EDUCATION: 0 or 1 year		-0.359 (0.00)		-0.053 (0.74)	
RESIDENCE: Atole		0.329 (0.00)			
BREASTFEEDING VARIABLES					
Medium frequency (8-11 times)		-0.370 (0.00)			
High frequency (12+ times)		-0.894 (0.00)			
Low intensity nursing		0.246 (0.05)			
MOTHER'S NUTRITION					
BMI>20		0.260 (0.02)			
High caloric intake		0.383 (0.00)			
CHILD'S NUTRITION					
Poorly nourished		0.226 (0.04)			
MOTHER'S HEALTH					
No morbidity		0.016 (0.91)			
CHILD'S HEALTH					
No morbidity		-0.100 (0.30)			
ENERGY EXPENDITURE					
Agric. and manual workers		-0.587 (0.00)			
Merchants, skilled workers		0.217 (0.04)			
Partial log L	-197	-2174	-66	-478	-162
Chi Square	7	418	16	8	6
d.f.	1	26	1	6	1
N	29	617	16	261	101

(*) p-values are shown in parentheses

Figure 1: A multiple state model of transitions to menses



FB= Fully Breastfeeding, **PB**= Partially Breastfeeding, **W**= Weaned,
D= Infant Death, **M**= Menses

Appendix 1

Definitions of Main States and Variables

The variables included in the analysis can be classified into seven groups: menstrual, breastfeeding, nutritional status, health status, energy expenditure, and demographic and socioeconomic conditions.

1. Postpartum amenorrhea

The length of postpartum amenorrhea is defined as follows: (1) the number of months elapsed between birth and the first incidence of at least two consecutive menstrual episodes within the first three months after delivery, or (2) the number of months elapsed between birth and the first menstrual episode when menses occurred beyond the third month after delivery, or (3) the number of months elapsed between a birth and the subsequent conception when menses never resumed. The first two cases represent the occurrence of the event of interest while the last case corresponds to a censored observation (58).

2. Breastfeeding variables.

Patterns of breastfeeding are defined according to three different sets of measures: breastfeeding status, which defines the type and duration of lactation; frequency of breastfeeding, which measures the number of times a day a child nurses; and an indicator for intensity of breastfeeding. The first and third covariates are time dependent covariates while the second is fixed.

2.1 Breastfeeding status. In this study, breastfeeding status is represented by four time-dependent covariates: full breastfeeding (FULL), partial breastfeeding (PARTIAL), weaning (WEAN), and infant mortality (DEATH). In contrast to other studies, the "effects" of infant mortality on resumption of menses are explicitly included in the models. In theory, the "effect" of infant mortality should be similar to that of weaning because since the death of the infant implies complete termination of breastfeeding.

2.2 Frequency of breastfeeding. The second breastfeeding covariate is represented by four fixed categories: low frequency (1-7 times a day), medium frequency (8-11 times a day), high frequency (12 or more a day), and a fourth category that collects missing values.

2.3 Intensity of breastfeeding. The third breastfeeding covariate, child's clinical supplementation, is an indicator that serves to proxy for intensity of breastfeeding. High intake means low intensity nursing. The indicator is defined as the amount of kilocalories (kcal) per day ingested by children who attended the INCAP's supplementation centers. Three categories were included: low intake (34.25 kcal. per day or less), high intake (more than 34.25 kcal. per day), and a third category that represents the missing values for this variable.

3. Variables for nutritional status

In order to assess the effects of a woman's nutritional status on resumption of menses, three variables are used: body mass index (BMI), which assesses chronic energy deficiency, and maternal energy intake, which measures current nutritional status. These covariates are time-dependent covariates. The effect of child nutritional status is assessed by the so-called height by age indicator, which measures protein-energy deficiency among children.

3.1 Mother's body mass index. The effects of mother's nutritional status on the resumption of menses in this study are primarily measured by the so-called body mass index, or BMI. In this analysis, three categories are considered: BMI less than 20 (some degree of malnutrition), BMI more than 20 (from normal to obese), and a third category to accommodate missing values.

3.2 Maternal energy intake. A third measure of nutritional status consists of information about mother's energy intake from INCAP supplementation. This indicator reflects the amount of supplementation intake and we express it in kilocalories (kcal) per day for mothers who went to INCAP's centers. Three categories were defined: high intake, low intake, and missing values.

3.3 Child's nutritional status. To assess child nutritional status we use a very common indicator, height by age (ht/age). Three categories were defined: poorly nourished, adequately nourished, and one for missing values.

4. Health variables

The data gathered on morbidity consists of symptoms of illness that mothers reported for themselves and their children and that correspond to episodes taking place two weeks before the interview. Information is also available on the number of days that women and children experienced some symptoms of illness during the month prior to the survey. Symptoms such as anorexia, apathy or irritability, and fever are considered among the **severity symptoms**. The indicators for mother's and child's health status are the monthly cumulative number of days spent ill. The categorization of these is as follows: no morbidity (zero days of illness), some degree of severity (one or more days of illness). A third category collects missing values.

5. Energy expenditure variable

Women's physical labor is captured by identifying work activities they performed on a daily basis. Different types of work activities reflect distinct levels of energy expenditure and therefore, allow us to differentiate the 'stress-load' these activities exert on the reproductive system. We expect their effects to be important if the hypothesis is, indeed, correct that high energy expenditures disrupt the functioning of the neuroendocrine system by affecting the normal release of GnRH. We defined four categories for **Mother's work patterns**: (i) women who reported no work outside the home (housewives), (ii) agricultural and manual workers, (iii) craftswomen, merchants and skilled workers,

and (iv) women who did not provide any information about their occupation. The first and the third occupational categories involve non-strenuous work activities and the expenditure of energy is considerably lower when compared to agricultural and heavy manual work, where strenuous physical labor is always present.

6. Demographic variables

Age of mother and birth order of child (parity) have important biological and behavioral effects of their own on the menstrual interval. In our analysis, however, we use them as controls for potentially confounding influences.

6.1 Parity. Parity is defined as the number of live births the woman had at the date of the survey, that is, the birth order of the child being studied. The categories are three: (i) women with one child, (ii) women with two or three children, and (iii) women with four or more children.

6.2 Mother's age. Mother's age is defined as the last birthday at the time of the birth of the last child. Three groups of women are considered, (i) mothers who were 19 years old or younger at childbirth, (ii) mothers who were between 20 and 29 years old, and (iii) those who were 30 years or more.

7. Socio-economic variables

Although socioeconomic characteristics of the woman can be expected to influence resumption of menses primarily through breastfeeding, nutritional and health status, we include them in the model to determine whether they have any residual impact on menses, to the extent the intermediate variables are imperfectly measured.

7.1 Mother's education. Mother's education was defined as the number of years the woman spent in school. Women were grouped into three categories: (i) women with low or no education (none or one year of formal instruction), (ii) women with a higher education (two or more years in school), (iii) and women with no information about this characteristic.

7.2 Mother and child residence. Finally, we take advantage of the INCAP study design and include an indicator of residence that distinguish mothers who reside in a village where INCAP administered special dietary supplementation (*atole* villages) from those living in control villages supplied with lower grade supplementation (*fresco* villages).