Parametric Frailty and Shared Frailty Models Applied to Waiting Time to First Pregnancy

Najaf Zare and Fariba Moradi

Abstract—Lifestyle, occupational and environmental factors have been suggested to affect the female reproduction. In the present study the effects of several such factors are investigated to waiting time to first pregnancy by frailty models. Information on waiting time to first pregnancy (WTTFP) was available on 882 women randomly selected from the rural population (south of Iran). Only the first pregnancy of each woman and only planned pregnancies were included. Frailty and shared frailty models were used to determine which factors had the most impact on WTTFP. The median WTTFP was 6.4 months. The height, age at marriage and menstruation regularity seemed more important predictors of WTTP.

Keywords—Fertility, Frailty models, Time to pregnancy.

I. INTRODUCTION

In the medical field frailty is a term that is used more frequently. It originates from gerontology where it is used to indicate that frail people have an increased risk for morbidity and mortality [1]. Frailty is a random component designed to account for variability due to unobserved individual-level factors that is otherwise unaccounted for by the other predictors in the model. All the parameter estimates are altered with the inclusion of the frailty [2].

Waiting time to first pregnancy (WTTFP) is an important problem that contributes substantially to population growth. The time it takes for a couple from initiating attempts to become pregnant until conception occurs (time-to-pregnancy) is gaining importance as a measure of natural fecundity [3].

Although more is known about the extent to which TTFP is associated with certain characteristics of the women, there are limited studies in rural district, especially in Iran and very rare studies with accurate statistical analyses. In the present study the effects of several such factors are investigated to the waiting time to first pregnancy by frailty models.

II. METHODS AND MATERIALS

A. Data

In a cross sectional study the fertility history of 1200 women in rural area of Shiraz (south of Iran) were studied. The women were selected by multistage random sampling from the list of villages. The first planned pregnancy were included in this study (n = 882). Data were gathered on age at marriage, education level, menstrual age, family income being enough, women’s height, age of marriage and regularity of menstruation before the first pregnancy. Furthermore, within a rural subsistence based society, the economic condition of any household is unlikely to fluctuate drastically from each other. Women do not work heavily in the fields, smoking habit is negligible and alcohol consumption is none or very rare.

B. Statistical Methods

Survival analysis characterized by censoring and truncation. The response variable T is time to some event. Parametric survival models assume some function form for baseline hazard, h0(t), and hence for S0(t). For example, Weibull proportional hazard (PH) model takes h0(t) = pt−1, and requires the additional estimation of the shape parameter p. Cox regression is a PH model that makes no assumption about the functional form of h0(t).

(i) Frailty models: Parametric specification plus covariates can only explain the variability in observed time to failure. A frailty model attempts to measure the unexplained variability as a latent multiplicative effect on the hazard function, i.e. the hazard becomes

h(t | α) = αh(t) and consequently S(t | α) = [S(t)]α .

A convenient choice for the distribution of the αs is the one-parameter gamma distribution with mean one (for purpose of model identifiability) and variance θ:

\[ g(\alpha) = \frac{\alpha^{\theta-1} \exp(-\alpha / \theta)}{\theta^\theta \Gamma(1/\theta)} . \]

With frailty models, we distinguish the individual level or conditional survival function S(t|α) from the population level or unconditional survival function S(t), which represents a population average.

\[ S_t(t) = \int_0^\infty S(t | \alpha) g(\alpha) d\alpha = [1 - \theta \ln(S(t))]^{-\theta} \]

and \[ h_t(t) = -\frac{dS_t(t)}{S_t(t)} \].

The log-likelihood is formed as a combination of failure and censored observations:

\[ \ln L = \ln \prod_{i=1}^n \left[ \frac{[S(t_i)]^{1-\delta} [S(t_i)]^{\delta}}{[S(t_i)]^{\delta}} \right] + \sum_{i=1}^n \left[ \ln S(t_i) - \ln S(t_i) + \delta h_t(t_i) \right] \]
where \( i = 1, 2, \ldots, n \) with \( i \)-th observation correspond to time span \((t_0, t_i]\) with either failure (\( \delta_i = 1 \)) or right censored (\( \delta_i = 0 \)) at time \( t_i \) [1], [2], [4].

(ii) Shared Frailty: With this model, clusters of subjects (in this study, villages) are assumed to share the same frailty. For the \( j \)-th observation in the \( i \)-th group, a shared frailty for Weibull PH regression has the form:

\[
h_{ij}(t \mid \alpha_i) = \alpha_i h_{ij}(t \mid x_j) = \alpha_i \exp(x_j \beta) pt^{-1}^{\alpha - 1} \quad j = 1, 2, \ldots, n_i, \quad i = 1, 2, \ldots, n
\]

i.e., the frailty is shared among the group (latent common group effect). This gives the interpretation that; individuals in a group \( i \) with \( \alpha_i > 1 \) are more frail (at higher risk). The conditional survival function is

\[
S_{ij}(t \mid \alpha_i) = [S_{ij}(t)]^{-\alpha} = \exp[-\alpha_i \exp(x_j \beta)t^\alpha]
\]

The estimate for the variance parameter \( \theta \) in a shared frailty model can be thought of as a measure of the degree of correlation, where \( \theta = 0 \) indicates no within-cluster correlation. The parameter \( \theta \) provides information on the variability (the heterogeneity) in the population of clusters [1], [2], [4].

We used the frailty and shared frailty models for the WTTFP. We used median or mean ±SD for descriptive statistics. Statistical analysis was done by SPSS release 16 and Stata release 10 software.

### III. RESULTS

The mean age of women was 32.1± 8.2 years and at marriage 18.4±4.0 with marriage duration 13.8±9.2 (range 0-39.3). The median WTTFP was 6.4 months (inter-quartile range=15). Increasing age at marriage decreased WTFP (\( r = - .126, p=0.001 \)) but increasing age at first conception increased the WTTP (\( r = .332, p<0.001 \)). Those with regular menstruation had more chance of conception (Figure 1).

The results of non-frailty, frailty and shared frailty models are shown on table 1. The maternal education, height, regularity of menstrual and age at marriage covariates seemed more related to WTTFP, and were selected to include in the models. The estimated \( \theta \) in table 1 is significant (by likelihood ratio test, \( p<0.001 \)) which indicates the presence of heterogeneity and necessitate the frailty models.

The estimated hazard ratio for menstruation using gamma frailty model is about 2. This is the estimated hazard ratio for two individuals having the same frailty in which one with regular menstruation and the other with irregular menstruation controlling for the other covariates in the model. In other words a woman with regular menstruation is two times more probable to conceive at any time \( t \) compared to a counterpart woman with irregular menstruation. In frailty model, for a given individual, the risk of entering to conception at waiting time \( t \) when in regular menstruation is about 1.7 times the risk when irregular menstruation in the same cluster.

### IV. DISCUSSION

Fertility was measured using time to pregnancy (TTP). It has been found that this is a useful tool when assessing reproductive effects [5] and that data can be collected retrospectively by using self-administered questionnaires, even when the recall times are as long as 14 years [6]. In the present study, several factors were found to have an impact on TTP. However, only regularity of menstruation, age at marriage and height of women had significant roles in models. Furthermore, height and age at marriage played somehow different role in two last models.

The disadvantage of parametric models is that they are not flexible in describing for example changes in the shape of the hazard function, e.g., Weibull hazards are monotone by definition. Parametric models can be made more flexible if we divide the time axis in intervals and allow the parameters of the model to be different on each interval (piecewise models) [1]. The Pareto distribution for TTP was used and discussed by Keding et al as satisfactory parametric model [7].

A major critique concerning retrospective TTP studies has been the exclusion of women who never conceived. However, the strength of the present study is that we also included women who had tried to conceive but so far had failed to do so. In addition to various biases inherent in retrospective assessment, a major limitation is the inability to accommodate the effects of sexual behavior, namely, the association between the conception probability and the timing of intercourse in relation to ovulation. To study factors related to biological fecundity and sterility, independent of behavioral factors, well-designed prospective studies of TTP are needed.

![Fig. 1 Kaplan–Meier plot of time to first pregnancy for irregular (upper curve) and regular (lower curve) menstruation](image-url)
### TABLE I

**RESULTS OF WWWFP BY WEIBULL REGRESSION WITH NO-FRAILTY, FRAILTY AND SHARED FRAILTY**

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>No frailty</th>
<th>Frailty</th>
<th>Shared frailty</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR</td>
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<td>p-value</td>
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<td>Education</td>
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<td>.439</td>
</tr>
<tr>
<td>Height</td>
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<td>.003</td>
<td>.013</td>
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<td>Age at menstruation</td>
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<td>.115</td>
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<tr>
<td>Regular menstruation</td>
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<td></td>
</tr>
<tr>
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**REFERENCES**