RESEARCH ARTICLE OPEN ACCESS

# Weibull Distributions for the Preterm Delivery

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**Abstract**
The purposes of this study are to evaluate the levels of CRH at pregnancy by using Weibull distributions. Also this study found the rate of change in placental CRH and the level of maternal cortisol in preterm delivery by the mathematical formulas.
**Keywords:** Cortisol, Corticotrophic-releasing hormone (CRH), Delivery, Mixture distribution, Pregnancy, Weibull distribution.

## I. Introduction

The probability density function (pdf) of a 2-parameter Weibull distribution is [1,8],

$$f(x:\alpha,\beta)=\frac{\alpha(x)^{\alpha-1}}{\beta^{a}}\exp(-\left(\frac{x}{\beta}\right)^{\alpha}) \text{ for}$$

$$0\le x<\infty \quad (1)$$

and for a 3-parameter Weibull distribution is

$$f(x:\alpha,\beta,\gamma)=\frac{\alpha(x-\gamma)^{\alpha-1}}{\beta^{a}}\exp(-\left(\frac{x-\gamma}{\beta}\right)^{\alpha}) \quad \text{for}$$

$$\gamma\le x<\infty \quad (2)$$

where $\alpha$, $\beta$ and $\gamma$ are the shape, scale and location parameters respectively.

A mixture distribution is a distribution made of combining two or more component distributions [8]. The probability density function of this mixture distribution can be shown as:

$$f(x)=w_1 f_1(x)+...+w_n f_n(x) \qquad w_i>0, \text{ and}$$

$$\sum_{i=1}^{n} w_i=1$$

where $w_i$ is the mixing parameter which represents the proportion of mixing of the component distributions. The function $f_i(x)$ is the probability density function of the component distribution $i$. While $n$ is the number of component distributions being mixed [10].

The probability density function of the mixture Weibull distribution of the two distributions in (1) and (2) is as follows;

$$f(x)=\frac{\alpha_1(x)^{\alpha_1-1}}{\beta_1^{\,a}}\exp(-\left(\frac{x}{\beta_1}\right)^{\alpha_1})+(1-w)\frac{\alpha_2(x-\gamma_2)^{\alpha_2-1}}{\beta_2^{\,\alpha_2}}\exp(-\left(\frac{(x-\gamma_2}{\beta_2}\right)^{\alpha_2}) \quad (3)$$

where, $\alpha_1,\alpha_2,\beta_1,\beta_2>0\le\gamma\le x$ and $0<w<1$. Here $w$ is the mixing parameter.

As a result, when the two sub-populations are given by equation (1), the model is characterized by five parameters, the shape and scale parameters for the two sub-populations and the mixing parameter $w$; with $0<w<1$.

The probability density function and failure rate of the two-fold Weibull mixture are given by;

$$f(x)=wf_1(x)+(1-w)f_2(x) \quad \text{and}$$

$$h(x)=\sum_{i=1}^{n} w_i(x)h_i(x)$$

where $w_i(x)=\dfrac{w_iR_i(x)}{\sum_{i=1}^{n} w_iR_i(x)}$ and $\sum_{i=1}^{n} w_i(x)=1$

and

$$R_i(x)=1-F_i(x)$$

$R_i(x)$ is the reliability function, Hence

$$h(x)=\frac{wR_1(x)}{wR_1(x)+(1-w)R_2(x)}h_1(x)+\frac{(1-w)R_2(x)}{wR_1(x)+(1-w)R_2(x)}h_2(x)$$

[10] who assumed that only the mixing proportions are unknown for the two component case;

$$f(x)=wf_1(x)+(1-w)f_2(x)$$

By integrating a family of equations of the form;

$$F(x)=wF_1(x)+(1-w)F_2(x)$$

which leads to the following

$$w=\frac{F(x)-F_2(x)}{F_1(x)-F_2(x)}$$

This gives necessary and sufficient conditions on $F_1$ and $F_2$ for the uniform attainment of the Cramer-Rao bound on the variance of $w$.

## II. Application

Remarkable surveillance and response systems have evolved and are conserved so that many species

from the desert dwelling Western Spade foot tadpole to the human fetus can detect threats to survival and adjust their developmental trajectory [2, 9]. Rapidly evaporating pools of desert water result in elevation of a stress hormone, corticotrophic-releasing hormone (CRH), in the pathway between the brain and the pituitary gland (median eminence) of the tadpole, precipitating metamorphic climax to escape imminent peril [3, 4]. If the CRH response is blocked during environmental desiccation, then the rate of development is arrested and the tadpole's survival is compromised.

The human fetus has evolved similar mechanisms to acquire information about the environment the guide its development. The human placenta is both a sensory and effector organ that incorporates and transduces information from its maternal host environment into the fetal developmental programs. It has receptors and expresses the genes for major stress systems, including the endocrine system and specifically CRH [5]. Placental CRH production increases dramatically over the course of normal human gestation [7] reaching levels at term observed only in the hypothalamic portal system (median eminence) during physiological stress. Abnormally accelerating rates or excessive levels of placental CRH are significant risk factors for an earlier onset of spontaneous birth. Because of this, CRH is proposed to regulate a placental clock that controls a cascade of physiological events leading to parturition. Despite general agreement concerning the significance of CRH for the timing of spontaneous birth, there is uncertainty about when CRH exerts its effects on human parturition [7] and what regulate the CRH surge.

CRH, a 41-amino acid neuropeptide, is synthesized primarily in the paraventricular nucleus of the hypothalamus and has a major role in regulating pituitary-adrenal function and the physiological response to stress. During pregnancy, CRH also is synthesized by the placenta. Placental CRH is identical to hypothalamic CRH in structure, immunoreactivity and bioactivity. In contrast, however, to the inhibitory influence on the promoter region of the CRH gene in the hypothalamus, maternal stress signals (glucocorticoids) from the adrenal glands activate the promoter region in the placenta and stimulate its synthesis. This positive feedback system contains both a signal to the fetus (elevated glucocorticoids) that the host environment (the mother) is threatened [11], potentially compromising fetal survival, and a response from the fetus (increased placental CRH production) that shortens gestation. The purpose of this study is to determine the critical intervals during which CRH influences the length of human gestation.

## III. Methodology

The sample was comprised of 203 adult women (over 18 year age, mean age = 29.9 years) consecutively recruited. Women also were excluded if they presented with any condition that could disregulate neuroendocrine function, such as endocrine, hepatic or renal disorders or the use of corticosteroid medications. Interviews assessed health behaviors to exclude women who smoked or consumed alcohol or drugs of abuse 6 months before and during the index pregnancy.

Women provided informed consent to be evaluated at four intervals during gestation; 13.5-16.6 (mean = 15.3), 17.8-20.5 (mean=19.2), 23.7-26.5 (mean=24.9) and 29.9-32.3 (mean 30.9) seeks gestation. A clinical ultrasound performed at the first and second intervals confirmed gestational age. Blood was collected at each interval for assessment of neuroendocrine profile. Women were followed to term and birth outcome information was abstracted from medical charts.

The HPA and placental stress axis was evaluated by assessing levels of B-endorphin (BE), ACTH, cortisol and CRH. CRH concentrations (pg/ml) were determined by radio-immunoassay (RIA; Bachem Penisula Laboratories, ScanCarlos, CA). Plasma samples (1-2 ml) were extracted with three volumes of ice-cold methanol, mixed, allowed to stand for 10 min at 4°C, and then centrifuged at 1700 × g for 20 min at 4°C by the modified method of Linton et al. [6].

Placental CRH increased significantly ($F_{3,210}$=106.48, pY < .0001, Greenhouse – Geisser correction) during pregnancy with rapidly accelerating levels after 25 seeks gestation (All pairwise comparisons p < .0001). Consistent with previous studies placental CRH levels in women destined to deliver preterm (before 37 weeks) had faster rates of increase ($F_{3,603}$=5.73, p < .001) [group × weeks gestation]) and significantly higher levels of CRH confined to the beginning of the early third trimester ($F_{1,201}$=5.53, p = .02 [post hoc comparison at 31 weeks]) than women who subsequently delivered at term (Fig.1)

Maternal levels of cortisol, ACTH and BE also increased significantly with advancing gestation (all p's < .0001). The two-fold increases in maternal ACTH and BE and the threefold increase in maternal cortisol were considerably less than the 25-fold increases in placental CRH through 31 weeks of gestation. Of these maternal measures, only cortisol distinguished women delivering term and preterm. This is the first evidence that levels of cortisol are higher as early as 15 weeks gestation ($F_{1,201}$Y=Y4.45, p=.03) with a similar trend at 19 weeks gestation ($F_{1,120}$Y=Y3.43, p=.065) in women who subsequently delivered preterm compared with women delivering after 37 weeks (Fig.2).

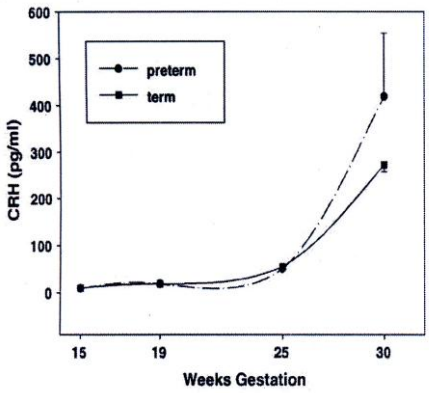


**Fig.1 – The rate of change in placental CRH between 26 and 31 weeks gestation is significantly faster and the level of placental CRH at 31 weeks gestation is significantly higher in women destined to deliver preterm.**

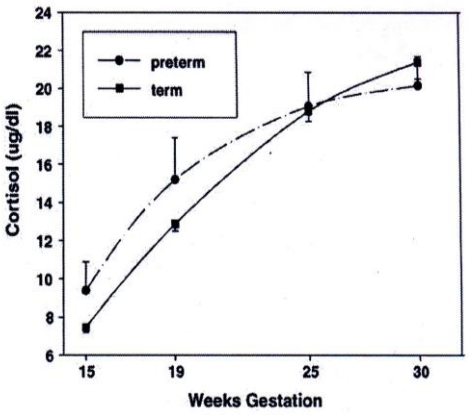


**Fig.2 – The level of maternal cortisol is significantly higher at 15 weeks gestation in women who will proceed to deliver before 37 weeks gestation (preterm).**

## IV. Mathematical Result

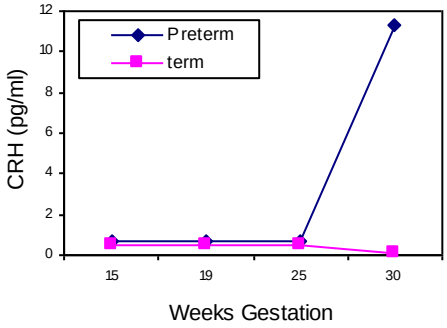


**Fig.3 – The rate of change in placental CRH Vs Time**

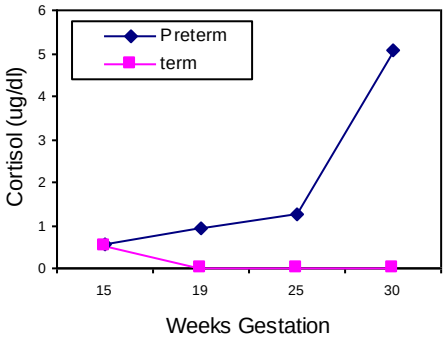


**Fig.4 – The level of maternal cortisol Vs Time**

## V. Conclusion

The mixture Weibull distribution is more useful as different values of the mixing parameter were used to obtain the estimation of the parameters. This study found that the rate of change in placental corticotrophic-releasing hormone (CRH) and the level of material cortisol have the major role in preterm delivery.

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