CHAPTER 8

COMPARISON OF GnRH ANTAGONIST VERSUS GnRH AGONIST IN MATHEMATICAL MODEL USING RELIABILITY GROWTH MODEL

8.1 Introduction

Reliability growth analysis is a set of mathematical tool that affords the ability to foresee fielded reliability. But effective reliability growth modelling is more than just mathematical and statistical procedures; it also incorporates processes for data collection, failure counting, effectiveness factor task and transformation of reliability growth results into expected counteractive practices. This thesis proposes a prototype to statistically scrutinize given data for complex biological problem.

A classification of failure types is presented and establish policies for evaluating data at different levels of the device. Moreover, a new method for trend analysis of failure data is proposed. Finally, introducing some assumptions based on the results of the analysis, and develop several new models to find the optimal inspection interval for a system subject to failures **[28].**

Controlled ovarian hyperstimulation (COH) coupled with in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) was one of the major advances in the treatment of subfertility in the second half of the 20th century. One aspect of COH-IVF or ICSI that requires attention is the occurrence of a luteinizing hormone (LH) surge which may occur prematurely, before the leading follicle reaches the optimum diameter for triggering ovulation. Such premature LH surges prevent effective induction of multiple follicular maturation patterns for a significant number of women.

Gonadotropin-releasing hormone agonists (GnRH AG) have played an important role in reducing the incidence of premature LH surges by reversibly blocking pituitary gonadotropin secretion **[31, 39].** As a result, the rate of cancellation of assisted conception cycles are decreased and pregnancy rates increased .However, the use of GnRH agonists is not without disadvantages. Even though the standard long GnRHa protocol proved to be the most efficacious protocol for theuse of GnRHa, it requires two to three weeks for desensitization with relatively high costs due to an increased requirement for gonadotropin injections and the need for hormonal and ultrasono graphic measurements **[41,77,99**].

Gonadotropin-releasing hormone antagonists (GnRH AT) have emerged as an alternative in preventing premature LH surges.In comparison with the GnRH agonists, the pharmacological mechanism by which GnRH antagonists

suppress the release of gonadotropins is completely different. While the agonists act by down-regulation of the pituitary GnRH receptors and desensitization of the gonadotrophic cells, the antagonists bind competitively to the receptors thereby preventing the endogenous GnRH from exerting its stimulatory effects on the pituitary cells. The competitive blockade of the receptors leads to an immediate arrest of gonadotropin secretion. This mechanism of action is dependent on the equilibrium between endogenous GnRH and the applied antagonist and is highly dose dependent, in contrast with the agonists **[30, 39, 85].**

While the first generation of GnRH antagonists showed allergic side-effects due to an induced histamine release, which hampered the clinical development of these compounds, third generation GnRH antagonists such as ganirelix and cetrorelix have resolved these issues and are approved for clinical use **[100,101]**.

Applying GnRH antagonists for pituitary down-regulation during COH is expected to result in a dramatic reduction in the duration of GnRH analogue treatment and to reduce the amount of gonadotropin needed for stimulation as compared with the long agonist protocol. Other potential benefits include a lower risk of developing severe ovarian hyper stimulation syndrome and avoidance of the oestrogen deprivation symptoms (for example sleepless, headaches) frequently observed in the pre-stimulation phase of a long agonist

protocol. Whether the previously mentioned benefits justify a change in routine treatment from the standard long GnRH protocol to the GnRH antagonist regimen depends on whether the clinical outcomes using these protocols are similar.

In this review focus is made on the safety and efficacy of a GnRH antagonist compared to GnRH agonist. Regarding the safety, a GnRH antagonist and significantly reduced the incidence of ovarian hyper stimulation syndrome (OHSS) by 50%. In addition, with GnRH antagonist treatment the chance of cancellation or coasting due to high risk to develop OHSS was only 52% of that with GnRH agonist treatment. The corresponding number needed to harm (NNH) was 26 with an absolute risk reduction of 5%. This means that for every 26 women undergoing down-regulation by agonist you would expect one more case of severe OHSS. In addition, the cancellation rate due to the high risk of developing OHSS was significantly higher in the GnRH agonist group.

This means that the difference would be highly significant without cancellations. So, a GnRH antagonist is safer than a GnRH agonist. Secondly, regarding effectiveness, the previous version of this review, reports that the GnRH antagonist down-regulation protocol was associated with a lower clinical pregnancy rates. However, there was no evidence of a difference in the live birth rate with GnRH antagonist. There are several possible explanations for the lower clinical pregnancy rate with antagonist.

Changes in study of outcomes can possibly be explained by factors which might have changed over time, such as the GnRH antagonist protocols used, incidence of LH instability and OC pre-treatment. Earlier performed Meta analyses showed a trend towards better clinical pregnancy rates (but not live birth), when using the fixed GnRH antagonist protocol. A smaller difference in LH instability in antagonist versus agonist cycles could possibly explain the differences in pregnancy results between the previous and the present versions of the review. The reason for the decrease in incidence of LH instability is, however, unclear **[146].**

The fact that in the subgroup analysis of studies not applying OC pre-treatment the difference between antagonist and agonist cycles was not significant stresses the fact that OC pretreatment should be considered a universally reliable approach in ovarian stimulation for assisted reproductive technology. More experience with the relatively new GnRH-antagonist protocol in large studies may positively influence the probability of pregnancy in antagonist cycles.

This would lead to more favorable study outcomes of the GnRH antagonist in large studies compared to small studies. Moreover, the relative inclusion of small and large studies in this review and the change in the learning curve over the last 10 years have not changed compared to preceding version. A decrease in the relative incidence of LH instability can possibly have improved

pregnancy outcomes in antagonist cycles. This observation warrants the strive for improvement of the LH suppressive effects of the antagonist co-medicated stimulation protocols **[85, 99].**

8.2 Notation

λ	Scale parameter for model
β	Shape parameter for model
t	Test time
T	Total test time
MTBF	Mean time between failures
GnRH AT	GnRH antagonist
GnRH *AG*	GnRH agonist
X_i	The i^{th} successive failure time
N	Total number of failures
λ_{AT}	Type AT modes failure intensity
λ_{AG}	Type AG modes failure intensity

λ_p Projected failure intensity

M_P Projected MTBF

8.3 Mathematical model and Assumptions

A classification of failure types is presented and policies are established for analyzing data at different levels of the device. Moreover, a new method for analysis of GnRH antagonist and GnRH agonist failure data is proposed. However, the application of all these techniques and models to medical devices is new.

The new definitions of Type GnRH antagonists and Type GnRH agonists models aligns the Extended reliability growth model to operational type failures where the GnRH antagonists modes will typically be due to human factor causes, and the Type GnRH agonists failure modes are typically due to hardware design and software design causes. This places more clarity and focus on the GnRH antagonists (allergic) and GnRH agonists (allergic) failure modes for analysis and management **[54, 77, 78].**

If human factor failures are not counted in the failure definition then most failures may be expected to be typically classified as GnRH agonists failure modes. The other key area that needs to be addressed is analyzing data across

test phases. This is the purpose of an additional parameter in the model. At the end of the test phase the basic extended model requires that all remaining Type GnRH agonists modes be corrected as delayed corrected actions.

This occurs with probability one. This is not required with the model presented in this paper. During a test phase ending at time T the Extended model for delayed corrected actions to be fixed before time T, at time T, or, in particular, after time T during a later test phase. The definition of "delayed" is expanded to include all Type GnRH agonists failure modes corrected [without side effects] after the time of failure but not necessarily at time T or before. Under this definition of a GnRH agonists mode it follows that whether or not a GnRH agonists mode seen during (0, T).

Patient-facing reliability growth analysis is a structured set of data collection procedures and mathematical techniques for measuring reliability (growth) with the objective of ultimately predicting patient -experienced reliability before the product is released. The premise of reliability growth (RG) is that a product's reliability improves as latent failure modes are discovered and failure intensity is reduced. The rate of RG improvement is proportional to the rate of occurrence of these failure modes. Improvement in Projected MTBF via failure mode discovery and corrective action can be calculated using mathematical models and statistical methods **[28, 54, 99,102].**

The system failure intensity is represented by a Non-Homogeneous Poisson Process (NHPP) and the resulting modeled data is fitted to mathematical expressions such as the Log linear functions.

The NHPP system failure intensity is given by

$$u(t) = \lambda\beta t^{\beta-1} \qquad 8.1$$

Where β is the shape parameter, when $\beta > 1$, the time between systems failures is decreasing which indicates negative reliability growth. When $\beta < 1$, the time between system failures is increasing which indicates positive reliability growth. When $\beta = 1$, the time between system failures is constant (no reliablity growth) and the expression for system failure intensity reduces to the Homogeneous Poisson Process (HPP).

$$\lambda = \frac{M}{T^{\wedge}\beta} \qquad 8.2$$

$$\hat{\beta} = \frac{M-1}{\sum_{i=1}^{n} \log \frac{T}{X_i}} \qquad 8.3$$

Time to First Failure	Failure Mode Status	Time to First Failure	Failure Mode Status
7	GnRH AT	56	GnRH AG
13	GnRH AG	60	GnRH AT
16	GnRH AG	63	GnRH AT
19	GnRH AG	64	GnRH AG
25	GnRH AT	68	GnRH AG
32	GnRH AG	73	GnRH AG
34	GnRH AT	76	GnRH AT
37	GnRH AG	78	GnRH AT
41	GnRH AG	80	GnRH AT
48	GnRH AT	82	GnRH AT
50	GnRH AG	83.5	GnRH AG
53	GnRH AT	84	GnRH AT

Table 8.1 **GnRH antagonist *failure mode and* GnRH agonist *failure mode***

For the data in table the system is tested for T=84 hours. There is a total of N=24 failures and all corrective action [no side-effects] will be incorporated at the end of the 84 hour test. Each failure is designated as either a Type AT failure mode or Type AG failure mode. There are n= 10 AT type A failure mode and m=14 AG failure mode **[28, 54, 78,99].**

$$\lambda^* = \frac{M}{T^{\wedge}\beta^*} \tag{8.4}$$

$$\beta^* = \frac{M-1}{\sum_{j=1}^{n} \log \frac{T}{X_j}} \tag{8.5}$$

If it is assumed that no corrective actions are incorporated into the system during $\beta < 1$ the test (no GnRH at failure modes), then this is equivalent to assuming that for λ_{CA} and λ^*_{CA} is estimated as in table **[34, 35].**

The estimated projected failure intensity

$$\lambda_p = \lambda_{AT} + \sum_{i}^{N} (1 - E_i) + \hat{E}h(T / AT) \tag{8.6}$$

$$\lambda^*_p = \lambda^*_{AG} + \sum_{i}^{N} \left(1 - E^*_i\right) + \hat{E}h(T / AG) \tag{8.7}$$

The extended model projected failure intensity is

$$\lambda_{EM} = \lambda_{CA} - \lambda_{AT} + \sum_{i}^{N} (1 - E_i) \frac{N_i}{T} + \hat{E}h(T / AT) \tag{8.8}$$

$$\lambda^*_{EM} = \lambda^*_{CA} - \lambda^*_{AT} + \sum_{j}^{N} \left(1 - E^*_j\right) \frac{N_j}{T} + \hat{E}h(T / AG) \tag{8.9}$$

The extended model projected MTBT is

$$M_{EM} = \frac{1}{\lambda_{EM}} \qquad M^*_{EM} = \frac{1}{\lambda^*_{EM}} \tag{8.10}$$

this outcome provides in section 8.4.

8.4 Results

Figure show the Mean time between failures between GnRH antagonists failure modes and GnRH agonists failure modes.

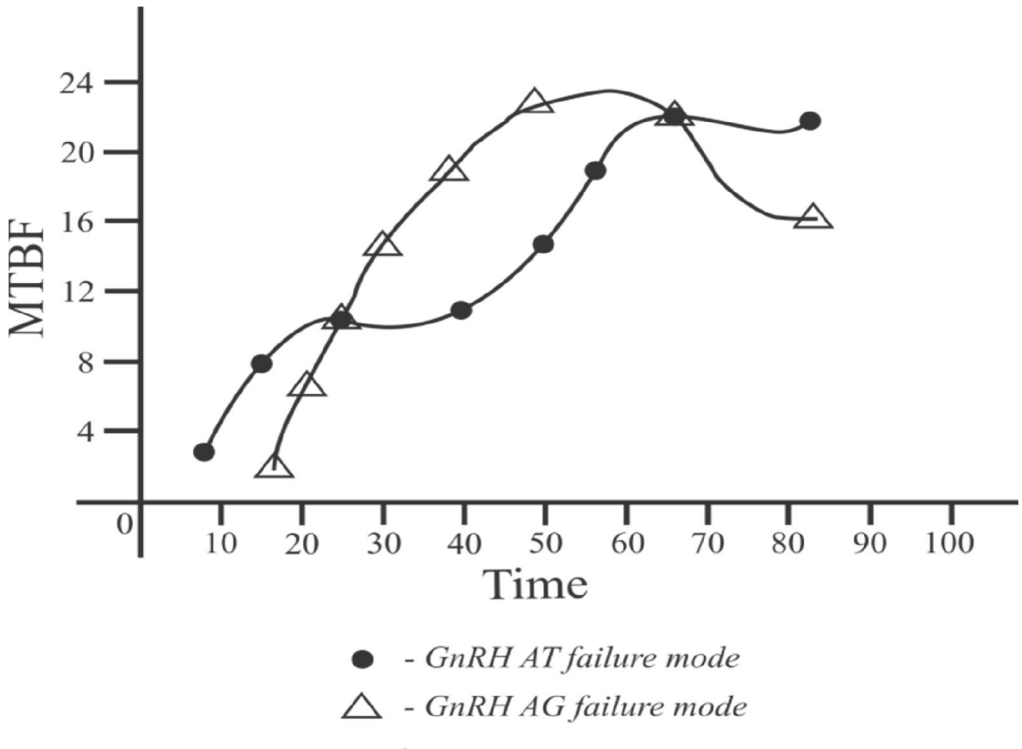

Figure 8.4.1 MTBF GnRH AT and GnRH AG

8.5 Conclusion

These calculation can be updated continuously throughout the entire reliability growth test and across the test phases, the model can be implemented using grouped data over the test phases. At the completion of the reliability growth test all remaining GnRH AT modes would be expected to be corrected. In conclusion, a protocol including a GnRH antagonist appears at least as effective as one using a GnRH agonist in patients who are poor responders on a long agonist protocol, and may be easier or more convenient to administer.

However, much work remains to be done in optimizing the GnRH antagonist protocols and individualizing these to different cycle characteristics. In the meantime, GnRH antagonist treatment may well be considered for patients not responding to a long GnRH agonist protocol. These results are encouraging for the design of further mathematical model aimed at evaluating the effect of such protocols on pregnancy rates in patients with poor ovarian response.