ANALYSIS OF INFERTILITY WITH REGARDS TO ASSISTED REPRODUCTIVE TECHNOLOGY

by

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ABSTRAK

Kaedah regresi telah menjadi satu komponen integral untuk sebarang analisis data berkenaan dengan memperihalkan hubungan antara pembolehubah sambutan dengan satu atau lebih pemboleubah penerang. Terdapat juga kes di mana pembolehubah kesudahan adalah diskrit dengan dua atau lebih nilai yang mungkin. Pada abad yang lalu, model logistik regresi telah menjadi suatu kaedah analisis piawai yang diguna dalam pelbagai bidang.

Objektif disertasi ini adalah untuk mencari penyesuaian model yang paling baik dan berparsimoni. Model tersebut juga mestilah bersesuaian secara biologi untuk menjelaskan perhubungan antara satu kesudahan (pembolehubah bersandar atau pembolehubah sambutan) dengan satu set pembolehubah tak bersandar (pembolehubah penerang atau pembolehubah ramal). Pembolehubah tak bersandar ini juga dipanggil sebagai kovariat.

Dalam kajian ini, data dikutip dari IVF Centre, Hospital Lam Wah Ee. Data ini terdiri daripada seramai 119 orang pesakit yang menjalani program *Assisted Reproductive Technologies* (ART), di mana teknik yang digunakan ialah *In-Vitro Fertilization* (IVF) dan *Intracytoplasmic Sperm Injection* (ICSI) sahaja. Daripada analisis yang diperoleh, kita mendapati bahawa ia mempunyai lebih daripada satu

kovariat yang boleh mempengaruhi keputusan ART. Selain daripada itu, kita juga mendapati bahawa bilangan pemindahan embrio perlu dipertimbangkan bagi pesakit-pesakit yang menjalani program ART. Ini adalah disebabkan bilangan pemindahan embrio akan meningkatkan kadar mengandung anak kembar.

ABSTRACT

Regression methods have become an integral component of any data analysis concerned with describing the relationship between a response variable and one or more explanatory variables. It is often the case that the outcome variable is discrete, taking on two or more possible values. Over the last decade the logistic regression model has become, in many fields, the standard method of analysis in this situation.

The goal of this dissertation is to find the best fitting and most parsimonious, yet biologically reasonable model to describe the relationship between an outcome (dependent or response variable) and a set of independent (predictor or explanatory) variables. These independent variables are often called covariates.

In this study, data were collected from IVF Centre, Hospital Lam Wah Ee, where 119 of patients underwent Assisted Reproductive Technologies (ART) program, the two techniques used are In-Vitro Fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI). From the analysis, we show that more than one covariate affect the outcome of ART. In addition, we found that number of embryo transferred has an effect on the chances of twin pregnancy.

CHAPTER 1

INTRODUCTION

1.1 Background of Case Study

Primary infertility is defined as a couple not conceiving after 12 months of regular unprotected sexual intercourse.

Infertility is a major problem affecting 15% of all married couples. Many of these infertile couples will never achieve a pregnancy with the usual infertility treatment. This is especially true with women who have blocked fallopian tubes and men with poor sperm count and function.

The discovery of Assisted Reproductive Technologies (ART) have provided hope for those couples whose chances of having their own children were previously considered to be hopeless.

The Assisted Reproductive Technologies are as below:

- In Vitro Fertilization (IVF)
- Intracytoplasmic Sperm Injection (ICSI)
- Testicular Sperm Aspiration (TESA)

- Gamete Intrafallopian Transfer (GIFT)
- Zygote Intrafallopian Transfer (ZIFT)
- Testicular Tissue Freezing
- Embryo & Sperm Freezing
- Egg & Sperm Donation Program
- Intrauterine Insemination (IUI)
- Semen Analysis
- Sex Selection

What do we mean by 'pregnancy'? Obviously the only success that really counts is the birth of a live baby. It is a great statistic to publish, but suffers somewhat because it takes nine months (or more) to obtain the birth information.

The simplest way of measuring success in any infertility treatment might be to record a positive pregnancy test. It is not a very good measure of 'success', however. It is very important to remember that not every woman, who has a positive pregnancy test, will go on to have a successful pregnancy. Many very early pregnancies fail ('miscarry', 'naturally abort') to develop.

1.1.1 IVF (In-Vitro Fertilization)

IVF is known to the public as "test tube baby" technique. In the procedure, the woman's ovaries are first stimulated for several days by special hormones to encourage growth of multiple eggs. Once produced, the eggs are extracted using a long needle inserted through the vagina under guidance of an ultrasound machine.

The eggs are then mixed with the husband's sperm (which had been washed and concentrated) in a plastic container to achieve fertilization. The fertilized eggs are now called embryos. The embryos are kept at body temperature in a special incubator to encourage growth. After 2-3 days, good quality embryos are then transferred to the woman's womb via a plastic tube introduced through her cervix. If successful, her pregnancy test will be positive at the end of 2 weeks.

1.1.2 ICSI (Intracytoplasmic Sperm Injection)

ICSI literally means injection of a sperm into an egg. To carry out ICSI the patient also undergoes the routine IVF procedure. The only difference is that instead of just mixing the eggs with sperms as in routine IVF and allowing the sperms to penetrate the eggs on their own; they will now inject 1 specially selected sperm into each individual egg. This is called ICSI.

ICSI requires a powerful microscope (magnification of 400x required) and "micromanipulators" to hold and move each egg and sperm. The needle used for injection is more than 7x thinner than the diameter of a human hair. Only 1 sperm is needed for each egg and therefore ICSI can be used for men with extremely low sperm count. In fact, even for some men with no sperm at all in their ejaculate, they are now able to extract sperms from their testes and use them successfully for ICSI.

1.2 Factors Affecting ART Pregnancy Rates

However, pregnancy outcome from ART depends on both partners. This includes their age, lifestyle, prior history of pregnancy in addition to the presence or absence of medical conditions.

There are many factors affecting the chances of pregnancy:

- The age of woman
- The number of embryos placed
- Whether the embryos are being used fresh or after freezing
- Semen analysis (sperm count & sperm motility)
- The stage of embryo development
- How many attempts these have already been
- The 'quality' of the embryo(s)
- Embryo transfer technique
- Ovarian stimulation
- Smoking

1.2.1 Female Factor Infertility

Delaying pregnancy is a common choice for women in today's society finding by ART Reproductive Center. The number of women in their late 30s and 40s attempting pregnancy and having babies has increased in recent years. At least 20 percent of women wait to begin their families after age 35. This is due to a number of factors, such as delaying childbirth until careers are established, waiting for a stable relationship, wanting to achieve financial security, or being unsure about the desire for parenthood. Also, information in the media about assisted reproductive technologies may give women an unrealistic sense of security that childbearing can be delayed.

It is important that women realize that age may affect their ability to conceive and have a healthy pregnancy. It is also important to be aware of possible tests and treatments which may be offered to older women to assist them in achieving pregnancy.

It is a biological fact that there is a decrease in fertility with advancing age. It is estimated that the chance of becoming pregnant in any one month is about 20 percent in women under 30, but only 5 percent in women over 40. Even with advanced infertility treatments, such as in vitro fertilization (IVF), fertility decreases and the chance of miscarriage increases in women after age 40. There are several explanations for this change in fertility, including medical conditions, changes in ovarian function, and alterations in the eggs released by the ovaries.

Aging does not just affect women. Though perhaps not as abrupt or noticeable as menopause for women, changes in fertility and sexual functioning do occur in men as they age. First, the ability to conceive decreases with aging. The testes tend to get slightly smaller and softer with age. Sperm morphology (shape) and motility (movement) also tend to decline. Despite these changes, there is no maximum age at which men are not capable of conceiving a child, as evidenced by occasions when men in their 60s and 70s conceive with younger partners. Sexual functioning in men may also change with aging. Often there is a slight decrease in a man's testosterone level which can cause a decrease in libido (sexual drive). Men may have difficulty achieving and/or maintaining erections as they age. These changes in testosterone, libido, and sexual functioning may not be strictly due to aging, but can be caused by illness, stress, or reactions to medications, all of which tend to occur more frequently as men get older. Furthermore, not all men experience significant changes in sexual function as they age, especially men who maintain good health over the years. If a man does have problems with libido or erections, there are treatments available and he should see a primary care physician or urologist to discuss his options.

As a woman ages, the remaining eggs in her ovaries also age, making them less capable of fertilization by sperm. In addition, fertilization of these eggs is associated with a higher risk of genetic disorders. For example, disorders involving the chromosomes, such as Down syndrome, are more common in children born to older women. There is a continuing increase in the risk of these chromosomal problems as women ages (Table 1.1). When eggs with chromosomal problems are fertilized, they are less likely to survive and grow. For this reason, women who are over 40 are at increased risk for miscarriage (Table 1.2).

The source of the decreased pregnancy rates in women over 40 is thought to be due, in large part, to the increase in the number of eggs with chromosomal problems. When eggs are collected from women in their 20s and 30s, fertilized, and placed in the uterus of a woman over 40, the chance for pregnancy in the older woman is much higher than she could expect if she had used her own eggs.

Table 1.1 Risk of Chromosomal Abnormality in Newborns By Maternal Age (*Créasy and Resnick,* 1994)

Maternal Age (years)	Risk for Down Syndrome	Total Risk for Chromosomal Abnormalities
20	1/1,667	1/526
25	1/1,250	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
41	1/82	1/53
42	1/63	1/42
43	1/49	1/33
44	1/38	1/26
45	1/30	1/21
46	1/23	1/16
47	1/18	1/13
48	1/14	1/10
49	1/11	1/8

Table 1.2 Risk of Miscarriage with Increased Age (*P.R Gindoff and R.Jewelewicz,* 1986)

Maternal Age (years)	Spontaneous Abortion (%)
15-19	9.9
20-24	9.5
25-29	10.0
30-34	11.7
35-39	17.7
40-44	33.8
≥45	53.2

1.2.2 Male Factor Infertility

The semen analysis is one of the most important tests in the infertility evaluation. It should be performed before any treatment of the female begins, as male factor infertility is present in 47% of infertile couples as announced by the ART Reproductive Center.

Several sperm characteristics are evaluated which include:

- Volume: This is a measure of how much semen is present in one ejaculation.
- Sperm count: This is a count of the number of sperm present per milliliter of semen in one ejaculation. Normal ≥ 20 million per milliliter
- Sperm motility: This is a measure of the percentage of sperm that can move forward normally. Ability to move or swim in a straight line. Normal ≥ 50%
- Sperm morphology: This is a measure of the percentage of sperm that have a normal shape. Normal ≥ 14% "highly normal forms"
- White blood cell count: White blood cells are not normally present in semen. Normal ≤ 5 white blood cells per microscopic field.
- Liquefaction time: Semen is a thick gel at the time of ejaculation and normally becomes liquid with 20 minutes after ejaculation. Liquefaction time is a measure of the time it takes for the semen to liquefy.
- pH: This is a measure of the acidity (low pH) or alkalinity (high pH) of the semen.

1.3 Fresh Embryo Transfer

Embryo transfer (ET) is usually done two or three days after egg collection. The ET is a simple procedure needing no medication and the partner is welcome to be present. A video screen shows the embryos prior to the scientist drawing them up into a catheter. The woman's legs are rested in stirrups and the catheter containing the embryos is passed through the cervix into the uterus. They are then flushed gently into the uterus. It takes only a few minutes and is usually about no more uncomfortable than having a pap smear.

After the ET there is no need to rest. Patient may go straight home or back to work and assume normal activity, including sexual relations. Keeping in mind that the patients are potentially pregnant, a healthy balanced lifestyle is recommended, and they are suggested to enjoy the normal life as anyone else who might be pregnant does until pregnancy is confirmed. This is often the most stressful part of the cycle, waiting for their period, waiting for the blood test, and wondering if 'she' is pregnant.

A pregnancy test is arranged for about 17 days after the transfer and this should be done even if a period arrives, to ensure there is no pregnancy hormone present. If the pregnancy test is positive, further blood tests or an ultrasound examination will be arranged as necessary. Occasionally a pregnancy can be present despite bleeding, and rarely this can be an ectopic pregnancy. An untreated ectopic pregnancy can cause severe complications and early diagnosis and treatment is very important.

1.3.1 Number of Embryos Replaced

The pregnancy rate is increased in an individual cycle by transferring more embryos. This has been a potential dilemma of IVF treatment since the very beginning. Whilst putting back more embryos at a single transfer gives more opportunities for at least one to successfully develop into a pregnancy, the disadvantage is clearly the risk of multiple pregnancies. Weighing up the pros and cons of one versus two embryos transferred is not a trivial matter. It is one of the most important decisions to be made during the IVF treatment.

If a couple choose to have two embryos transferred at each embryo transfer procedure they will, on average, achieve a pregnancy quicker, with fewer miscarriages, and less IVF treatment cost, when compared to single embryo transfers. Transferring embryos one-at-a-time, on average, takes more transfers than the same number of embryos two at a time; more cost; more disappointments; more time wasted.

The situation is made slightly more complex because the alternative of freezing extra embryos may eventually create somewhat fewer babies. It needs highly skilled procedure of freezing and thawing embryos. The freeze/thaw process, however, does have some impact on the embryo and its ability to develop into a baby no matter how well the process is carried out. If a woman has two high quality embryos following her egg collection procedure and chooses to freeze the second of those embryos, rather than transfer that embryo, Melbourne IVF (MIVF) has estimated that the second embryo's chance of developing into a baby in a subsequent freeze/thaw transfer will have been reduced by about 30%.

Many couples with long histories of fertility problems would see the birth of twins as blessing. There is no doubt that the birth of two babies may be great joy but it is important to remember that even twins are at increased risk of some childbirth problems. They are more likely to be born prematurely, to have low birth weight, to have cerebral palsy, and suffer a greater risk of dying at, or close to, birth.

Interestingly, IVF twins are not as prone to these problems as are non-IVF twins. This seems to be because identical ('monozygotic') twins dominate the poor-outcome statistic, and they are much more common in naturally conceived twins.

In the two years statistic report (1st Jan 2002 to 30th June 2004) from Melbourne IVF, if two embryos were transferred fresh in women aged less than 35 years, 35% had a foetal-heart pregnancy. Of these pregnancies, 34% had twin foetal hearts. It is too early to know how many healthy babies will be born. In contrast, if just a single embryo was transferred (402 transfers) the foetal heart pregnancy rate was 22% with only 1% twins. However, after weighing up these factors, most of the patients prefer to have two embryos replaced, at least for the first pregnancy.

Transferring two embryos effectively doubles the pregnancy rate for that attempt. Whilst there may be important qualifications with regard to embryo quality, in a practical sense, the greater the number of embryos transferred, the more likely you are to conceive. The biggest single advantage to transferring more than one embryo is to reduce the time to achieve a pregnancy.

In a fresh embryo transfer procedure, each extra embryo that is transferred does not have to go through a freeze/thaw cycle. It is estimated that there is a 30% reduction in pregnancy potential for each embryo that goes through the freeze/thaw cycle. The reason for this reduction in pregnancy potential is related to either none or partial survival of embryos after thawing.

The transfer of one embryo virtually eliminates the possibility of a twin pregnancy. It is possible however for that embryo to split and form a twin pregnancy. In this situation the twins are identical. Some pregnancy complications (MIVF's outcome) are increased in multiple pregnancies:

1. Perinatal motility is the measure of motility after 20 weeks pregnancy and less than 4 weeks following birth. The risk of perinatal motility increases with increasing numbers of fetuses in the uterus.

Perinatal mortality

Singleton	9.2/1000 births
Twins	42.9/1000 births
Triplets	145.5/1000 births

2. Intellectual or physical disability commonly referred to as cerebral palsy.

	12 Months	3 Years
Singleton	1.6/1000 births	2.3/1000 births
Twins	7.3/1000 births	12.6/1000 births
Triplets	28.0/1000 births	44.8/1000 births

3. Prematurely; average duration of pregnancy decreases with increasing number of fetuses.

Average duration of pregnancy:

Singleton	40 weeks
Twins	36 weeks
Triplets	33 weeks

1.4 Objectives and Outlines of Study

As discussed previously, there are many factors affecting the pregnancy outcome from ART program. The objective of this study is to ascertain if the variables were important in the population being served by the medical center (Hospital Lam Wah Ee) where the data is collected. In addition, we analyze whether chances of having multiple pregnancies through IVF/ICSI are much higher than natural conception. The data used in this study were collected from Hospital Lam Wah Ee, where 119 patients have undergone IVF & ICSI program in the year 2003.

This study is focused on the introduction to one of the applications of logistic regression model and its use in methods for modeling the relationship between a dichotomous outcome variable and a set of covariates.

This dissertation is divided into five chapters. The first chapter is an introduction to provide a brief insight into the background of the study. Chapter two is a focused introduction to the logistic regression model and its use in methods for modeling the relationship between a dichotomous outcome variable and a set of covariates.

Some literature review on background researchers have been discussed in chapter three. Chapter four covers the details on the case study analysis. This chapter analyzed the findings on which covariates contributes to the outcome of ART. In addition, it also includes the analysis of the cause of multiple pregnancies. These can be a guideline for those patients going for ART program. Chapter five discussed the overall conclusion and the significance of the present study. This chapter also provides some limitations of the present study and suggestions for possible modifications and additions that could be incorporated for improvement in future research.

CHAPTER 2

METHODOLOGY

2.1 Logistic Regression Model

Regression methods have become an integral component of any data analysis concerned with describing the relationship between a response variable and one or more explanatory variables. It is often the case that the outcome variable is discrete, taking on two or more possible values. Over the last decade the logistic regression model has become, in many fields, the standard method of analysis in this situation.

Before beginning a study of logistic regression it is important to understand that the goal of an analysis using this method is the same as that of any model building technique used in statistic: to find the best fitting and most parsimonious, yet biologically reasonable model to describe the relationship between an outcome (dependent or response variable) and a set of independent (predictor or explanatory) variables. These independent variables are often called covariates.

Consider a collection of p independent variables which will be denoted by the vector **x'** = ($x_1, x_2, \ldots, x_p$). For the moment we will assume that each of these variables is at least interval scaled. Let the conditional probability that the outcome is present be denoted by $P(Y=1 \mid x) = \pi(x)$. Then the logit of the multiple logistic regression models is given by the equation

$$g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p$$

in which case

$$\pi(x) = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}} \qquad (2.1)$$

2.2 Fitting the Logistic Regression Model

Assume that we have a sample of n independent observations of the pair (x_i, y_i), $i = 1, 2\ldots$ n, where y_i denotes the value of a dichotomous outcome variable and x_i is the value of the independent variable for the *i* subject. Furthermore, assume that the outcome variable has been coded as zero or 1, representing absence or presence of the characteristic, respectively. This coding for a dichotomous outcome will be used throughout the dissertation. To fit the logistic regression model in Equation (2.1) to a set of data requires that we estimate the values of β_0 and β_1, the unknown parameters.

The general method of estimation that leads to the least squares function under the linear regression model is called the maximum likelihood method. This method will provide the foundation for our approach to estimate with the logistic regression model. In a very general sense the method of maximum likelihood yields values for the unknown parameters which maximize the probability of obtaining the observed set of data. In order to apply this method we must first construct a function, called the likelihood function. This function expresses the probability of the observed data as a function of the unknown parameters. The maximum likelihood estimators of these parameters are chosen to be those values which maximize this function. Thus, the resulting estimators are those which agree most closely with the observed data.

If Y is coded as zero or one then the expression for π(x) given in equation (2.1) provides (for an arbitrary value of $\beta' = (\beta_0, \beta_1)$, the vector of parameters) the conditional probability that Y is equal to 1 given x. This will be denoted as P(Y = 1 | x). It follows that the quantity 1- π(x) gives the conditional probability that Y is equal to zero given x, P(Y= 0 | x). Thus, for those pairs (x_i, y_i), where $y_i = 1$ the contribution to the likelihood function is $\pi(x_i)$, and for those pairs where $y_i = 0$ the contribution to the likelihood function is 1- $\pi(x_i)$, where the quantity $\pi(x_i)$, denotes the value of π(x) computed at x_i. A convenient way to express the contribution to the likelihood function for the pair (x_i, y_i) is through the term

$$\zeta(x_i) = \pi(x_i)^{y_i}[1-\pi(x_i)]^{1-y_i} \tag{2.2}$$

Since the observations are assumed to be independent, the likelihood function is obtained as the product of the terms given in Equation (2.2) as follow:

$$\ell(\beta) = \prod_{i=1}^{n} \zeta(x_i) \tag{2.3}$$

The principle of maximum likelihood states that we use as our estimate of β the value which maximizes the expression in Equation (2.3). However, it is easier mathematically to work with the log of equation (2.3). This expression, the log likelihood, is defined as

$$L(\beta) = \ln[\ell(\beta)] = \sum_{i=1}^{n} \{y_i \ln[\pi(x_i)] + (1-y_i)\ln[1-\pi(x_i)]\} \qquad (2.4)$$

To find the value of β that maximizes L (β) we differentiate L (β) with respect to β_0 and β_1 and set the resulting expressions equal to zero. These equations are as follows:

$$\sum_{i=1}^{n}[y_i - \pi(x_i)] = 0 \qquad (2.5)$$

and

$$\sum_{i=1}^{n} x_i[y_i - \pi(x_i)] = 0 \qquad (2.6)$$

and are called the likelihood equations. In equation (2.5) and (2.6) it is understood that the summation indicated by $\sum$ is over i varying from 1 to n.

The value of β given by the solution to equation (2.5) and (2.6) is called the maximum likelihood estimate and will be denoted as $\hat{\beta}$. In general, the use of symbol ^ will denote the maximum likelihood estimate of the respective quantity. This quantity provides an estimate of the conditional probability that Y is equal to 1, given that x is equal to x_i. As such, it represents the fitted or predicted value for the logistic regression model. An interesting consequence of equation (2.5) is that

$$\sum_{i=1}^{n} y_i = \sum_{i=1}^{n} \hat{\pi}(x_i)$$

That is, the sum of the observed values of y is equal to the sum of the predicted (expected) values.

2.3 Testing for the Significance of the Coefficients

After estimating the coefficients, our first look at the fitted model commonly concerns an assessment of the significance of the variables in the model. This usually involves formulation and testing of a statistical hypothesis to determine whether the independent variables in the model are "significantly" related to the outcome variable.

The guiding principle with logistic regression is to compare observed values of the response variable to predicted values obtained from models with and without the variable in question. In logistic regression comparison of observed to predicted values is based on the log likelihood function defined in Equation (2.4). To better understand this comparison, it is helpful conceptually if we think of an observed value of the response variable as also being a predicted value resulting from a saturated model. A saturated model is one that contains as many parameters as there are data points.

The comparison of observed to predicted values' using the likelihood function is based on the following expression:

$$D = -2 \ln\left(\frac{\text{(likelihood of the current model)}}{\text{(likelihood of the saturated model)}}\right) \quad (2.7)$$

The quantity inside the large brackets in the expression above is called the likelihood ratio. The reason for using minus twice its log is mathematical and is necessary to obtain a quantity whose distribution is known and thus can be used for hypothesis testing purpose. Such a test is called the likelihood ratio test. Using Equation (2.4), Equation (2.7) becomes

$$D=-2\sum_{i-1}^{n}[y_i \ \ln\left(\frac{\hat{\pi}_i}{y_i}\right)+(1-y_i)\ln\left(\frac{1-\hat{\pi i}}{1-y_i}\right)] \quad (2.8)$$

where $\hat{\pi} = \hat{\pi}(x_i)$

The statistic, *D*, in Equation (2.8) is called the deviance, and plays a central role in some approaches to assess goodness of it. The deviance for logistic regression plays the same role as the residual sum of squares plays in linear regression.

For purpose of assessing the significance of an independent variable we compare the value of *D* with and without the independent variable in the equation. The change in *D* due to including the independent variable in the model is obtained as follows:

G = *D*(for the model without the variable) – *D*(for the model with the variable)

The statistic plays the same role in logistic regression as does the numerator of the partial F test in linear regression. Because the likelihood of the saturated model is common to both values of *D* being differenced to compute G, it can be expressed as

$$G = -2 \ln \left(\frac{\text{(likelihood without the variable)}}{\text{(likelihood with the variable)}} \right) \qquad (2.9)$$

For the specific case of a single independent variable it is easy to show that when that variable is not in the model, the maximum likelihood estimate of β_o is $\ln(n_1/n_0)$ where $n_1 = \sum y_i$ and $n_0 = \sum(1- y_i)$ and that the predicted value is constant, n_1/n in this case the value of G is as follow:

$$G=2\left\{\sum_{i=1}^{n}\left[y_i \ln(\hat{\pi}i) + (1-y_i)\ln(1-\hat{\pi}i)\right] - \left[n_1 \ln(n_1) + n_0 \ln(n_0) - n\ln(n)\right]\right\} \qquad (2.10)$$

Another similar, statistically equivalent test is suggested. This is the Wald test. The assumptions needed for this test is the same as those of the likelihood ratio test in equation (2.10).

The Wald test is obtained by comparing the maximum likelihood estimate of the slope parameter, $\hat{\beta}_1$, to the estimate of its standard error. The resulting ratio, under the hypothesis that $\hat{\beta}_1 = 0$, will follow a standard normal distribution. The Wald test for the logistic regression model is

$$W = \frac{\hat{\beta}_1}{S\hat{E}(\hat{\beta}_1)} \qquad (2.11)$$

The Wald (W) statistic normally will fix 2 as a critical value to assess the significance of the coefficients. If the W statistic for the coefficient exceeds 2, then we could conclude that the variables are significant. Hauck and Donner (1977) examined the performance of the Wald test and found that it behaved in an aberrant manner, often failing to reject when the coefficient was significant. They recommended that the likelihood ratio test be used.

CHAPTER 3

LITERATURE REVIEW

Jansen RP (2003) studied the effect of female age on the likelihood of a live birth from one IVF to determine the chance of at least one live birth from one round of IVF treatment and the effect of the woman's age on that likelihood. Design: Retrospective analysis of outcomes from IVF treatment which included embryos in the retrieval cycle. All IVF patients (median age, 36 years; range, 22-48 years) who attended a private IVF clinic in Sydney for egg retrieval between 1 Jan 1998 and 31 Dec 1998, and had embryo placements performed up to 30 June 2001. Measurement from main outcome found that independently audited live births surviving the neonatal period. Results showed 565 women had 648 egg retrievals during the period. The age of peak utilization of IVF was 39 years. For women aged 34 years or less, the chance of a live birth from one round of egg retrieval and IVF treatment was 52.4%. For women aged 35-44 years, there was a linear decline in the live birth rate, and no babies were born from retrievals at age 45 years and above. There was an age-dependent rise in the frequency of miscarriages, from 10.5% for those over 40 years ($P<0.01$). Conclusion: As fertility with IVF falls from the age of 34 years, and the age of peak IVF utilization is 39 years, many Australian women are seeking IVF at an age when the likelihood of a live birth is reduced.

Another research has been carried out by Ng et al (2001) showed that subjecting transfer of two embryos instead of three will not compromise pregnancy rate but will reduce multiple pregnancy rate in an assisted reproductive unit. Their objective was to compare the pregnancy rates and multiple pregnancy rates of cycles initiated in 1998 and in 1999, during which 3 and 2 embryos were advised to be replaced, respectively. Study Design with a retrospective study. Results showed there were no differences between 1998 and 1999 in the pregnancy rate per cycle started or per transfer, implantation rate and the multiple pregnancy rates, despite a significantly lower number of embryos replaced in 1999. A significantly higher implantation rate was found in cycles with frozen embryos than those without. Using logistic regression analysis, the chance of pregnancy was significantly improved only by the presence of frozen embryos in the fresh cycles with an odds ratio of 2.0 whereas the chance of multiple pregnancies was significantly increased by replacing 3 embryos instead of 2 (odds ratio: 2.1). Patients should be advised to have 2 embryos replaced without jeopardizing the pregnancy rates in the fresh cycles. The risk of multiple pregnancies is significantly increased when 3 embryos are transferred instead of 2.

Ravhon and Hurwitz (2002) pointed out that transfer of single embryo is a method to reduce twins pregnancy rate in IVF treatment. They introduced the high success rate in IVF treatment is followed by a high rate of multiple pregnancies. Over 30% of IVF pregnancies are multiples and carrying higher risk to the neonates compared with singleton pregnancy. Twin pregnancy is less dangerous than higher order multiple pregnancies but it has a significantly higher risk factor compared with singleton pregnancy. Therefore, it is crucial to find methods to reduce twin pregnancy rate. The goal of this review is to present the peril of twin pregnancy and to evaluate