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Review

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Success of *In Vitro* Fertilization: A Researched Science or a Performance Indicator

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Abstract

Divisions of reproductive medicine often perceive the live birth rate (LBR) as the single most important performance indicator for any infertility clinic, and it reflects on the quality of their services. Due to this perception, some infertility experts might refrain from disclosing these rates in publications as a researched science. Infertility experts might not be familiar with the various methods of reporting LBR as an outcome of *in vitro* fertilization (IVF) and therefore should be aware of these methods. Moreover, infertility experts might miss to take into account some couple and disease-related characteristics that could be successful determinants of this LBR. This is a brief review on infertility and its impact on married couples, as well as the history and description of IVF. We also present infertility experts with various methods of reporting LBR and shed light on some of the couple and disease-related factors associated with higher LBRs after IVF as reported in literature.

Keywords: Infertility; Live birth rate; Conditional; Cumulative; *In vitro* fertilization

Overview on Infertility

Infertility is an unanticipated medical condition that might take its toll, to a certain degree, on the psychological, social and financial welfare of married couples planning to conceive. The global prevalence of primary infertility based on nationwide surveys conducted in 190 countries and territories between 1990 and 2010 was 1.9% [1]. These were married couples in their reproductive age who failed to attain a live birth within the first 2 years of marriage [2]. The rate of secondary infertile couples, who previously had at least one live birth yet failed to reconceive again, is almost 10% worldwide [2]. The highest regional prevalence was observed in South Asia, followed by Sub-Saharan Africa, then North Africa/Middle East, then Central/Eastern Europe and Central Asia [1]. Once a reproductive problem or a delay in child bearing is suspected, some couples might engage in a debate on who is the affected partner, mostly aggravated by social stressors [3, 4]. One study noted that the use of females' ability to conceive, as a measure to differentiate between primary and secondary infertility, is however problematic as it places responsibility for a couple's infertility on the doorsteps of the female partner [5]. These couples will probably remain anxious until the actual etiology of their infertility is revealed.

Identifying the etiology of infertility is a demand for any infertility clinic. Significant improvements in technologies are now able to reveal whether the cause of infertility is medically diagnosed or otherwise unexplained. About one-third of infertility cases are caused by female infertility factor problems. Almost 30% of reproductive problems are due to the male infertility factor. The other cases are caused by both gender problems or by unknown ones [6]. Male infertility problems are related to the semen/sperm quality or quantity [7, 8]. Sperm abnormality is usually an early suspected cause of infertility; subsequently, an early semen analysis is common [9]. Although semen quality and testicular function decline with age [10], males are less likely to be the infertile partners (20-30%) [8]. Female infertility factor contributes to 30-40% of the cases, mainly due to ovulatory defects [8, 11]. In general, factors associated with infertility in females are diverse and circumstantial, such as the age, obstetrical history, unhealthy lifestyle, menstrual problems, body mass index, and other environmental factors [12].

The Mayo Infertility Care Clinic has stated a detailed list of causes and risk factors associated with male and female infertility (Table 1) [13]. Infertility experts unanimously consider age as one predicting factor for infertility in both genders of the couple [1, 14]. Two infertility clinics reported a mean age of 35 years among infertile males [14] and 32 years among infertile females [15]. Infertile couples are usually advised to begin investigation after 12 months of unprotected sex or after 6 months if the female partner is > 35 years or immediately if the cause of infertility or sub-fertility is known [16]. Studies reported that 10-13% of couples are reported to have secondary infertility, probably because those who try to conceive after the age 30 have already crossed the reproductive peak [17, 18].

IVF and LBRs

Infertility is not life-threatening, but its management is both complex and expensive. IVF dates back to 1968, and the first

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Table 1. List of Potential Causes and Risk Factors Associated With Male and Female Infertility as Issued by the Mayo Clinic Infertility Care

	Male infertility	Female infertility
Causes	• **Abnormal sperm production or function:** undescended testicles, genetic defects, health problems such as diabetes or infections such as chlamydia, gonorrhea, mumps or HIV. Enlarged veins in the testes (varicocele). • **Problems with the delivery of sperm:** sexual problems (premature ejaculation), genetic diseases (cystic fibrosis), structural problems (blockage in the testicle, damage or injury to the reproductive organs. • **Overexposure to certain environmental factors:** pesticides and other chemicals, radiation, cigarette smoking, alcohol, marijuana or taking certain medications, such as antibiotics, antihypertensives, anabolic steroids or others. Frequent exposure to heat, such as in saunas or hot tubs. • **Damage related to cancer and its treatment:** radiation or chemotherapy as treatment for cancer.	• **Ovulation disorders:** hormonal disorders such as polycystic ovary syndrome, hyperprolactinemia, hyperthyroidism, hypothyroidism. Excessive exercise, eating disorders, injury or tumors. • **Uterine or cervical abnormalities:** abnormalities with the opening of the cervix, polyps in the uterus or the shape of the uterus, noncancerous (benign) tumors in the uterine wall (uterine fibroids). • **Fallopian tube damage or blockage:** inflammation of the fallopian tube (salpingitis), pelvic inflammatory disease, sexually transmitted infection, or adhesions. • **Endometriosis.** • **Primary ovarian insufficiency:** early menopause. • **Pelvic adhesions:** bands of scar tissue that bind organs after pelvic infection, appendicitis, or abdominal or pelvic surgery. • **Cancer and its treatment.** • **Medical conditions associated with delayed puberty.**
Risk factors in both genders	• **Age:** Woman's fertility gradually declines with age, especially in her mid-30s, and it drops rapidly after age 37. Men over age 40 may be less fertile than younger men. • **Tobacco use:** Smoking tobacco or marijuana by either partner reduces the likelihood of pregnancy. • **Alcohol use:** For women, there's no safe level of alcohol use during conception or pregnancy. For men, heavy alcohol use can decrease sperm count and motility. • **Being overweight:** An inactive lifestyle and being overweight may increase the risk of infertility. A man's sperm count may also be affected if he is overweight. • **Being underweight:** Women at risk of fertility problems include those with eating disorders, such as anorexia or bulimia, and women who follow a very low calorie or restrictive diet. • **Exercise issues:** Insufficient exercise contributes to obesity, which increases the risk of infertility. Less often, ovulation problems may be associated with frequent strenuous, intense exercise in women who are not overweight.	

human baby following such assisted reproductive technology was born in 1978 [19]. In IVF, infertile couples usually undergo fresh, non-donor intracytoplasmic sperm injections, followed by the transfer of cells. In some cases, couples might request the assistance of a gestational carrier. Nowadays, IVF costs roughly $12,000 USD to $20,000 USD in the United States, depending on a range of tests and medications prescribed [20]. The cost of IVF in some countries tends to be less, such as that in Hong Kong ($10,000), Canada ($7,200), Australia ($5,200 - $7,000), Hungary ($3,700) and South Africa or Turkey ($3,000). A list of IVF estimated costs among other countries has been issued by the global IVF as of 2008 (Table 2) [21]. These costs include the fees paid for medical consultations, individual cycles of IVF and fertility drugs. It is worth mentioning that some couples might seek IVF treatments outside their home countries in attempt to cut off some of these expenses, but at the same time enduring travel expenses in what is known as medical tourism. Medical insurance coverage for infertility treatments varies, as some insurance plans will not cover such costs while others might pay part of it. One study stated that the coverage for assisted reproductive technologies is debated on whether fertility treatments should be accounted as a medical treatment for infertility as a disease or should it be accounted as an elective procedure [22].

International guidelines based on the recommendations of the American College of Obstetricians and Gynaecologists (ACOG), American Society for Reproductive Medicine (ASRM), Canadian Fertility and Andrology Society (CFAS), and Royal College of Obstetricians and Gynaecologists (RCOG), state that candidates eligible for IVF shall receive a standardized pre-cycle counseling package prior to the first IVF trial to maximize its success [23]. In addition, the European Society of Human Reproduction and Embryology (ESHRE) has stressed on an essential two-dimensional approach, both mental and medical health collaborative counseling, as many people with fertility problems desire psychosocial help as well [24]. An infertility counselor will advise both partners to quit smoking or alcohol consumption, limit the intake of caffeinated beverages, adhere to a healthy well-balanced diet, perform non-aggressive exercise and avoid hot tubs or saunas. They are also advised to report any signs indicative of a sexually transmitted disease such as herpes or fever 1 month prior to the trial. Couples are instructed to refrain from intercourse 3 - 4 days prior to the egg retrieval and following embryo replacement until the pregnancy is confirmed. Females are especially instructed to avoid all medications except for paracetamol/vitamins, while males are instructed to avoid tight underwear [25]. However, the compliance of infertile couples with these

Table 2. A Comparison of Estimated IVF Cost Chart in Different Countries

Country	Cost as of August 2008	Country	Cost as of August 2008
Argentina	$4,160	Latvia	$2,500
Australia	$5,200	Lebanon	$6,475
Austria	$3,600	Lithuania	$3,500
Canada	$7,200	Malaysia	$3,400
China	$2,400	Netherlands	$2,598
Czech Republic	$2,500	Norway	$3,200
Denmark	$4,000	Pakistan	$1,618
Dominican Republic	$8,300	Portugal	$4,000
Finland	$3,267	Qatar	$2,800
Greece	$4,300	Russia	$3,400
Hong Kong	$10,000	Saudi Arabia	$6,475
Hungary	$3,700	Singapore	$7,284
Iceland	$5,026	South Africa	$3,000
India	$3,238	Spain	$5,600
Indonesia	$4,856	Sweden	$8,000
Iran	$5,200	Switzerland	$3,700
Israel	$4,856	Taiwan	$4,856
Italy	$3,150	Thailand	$3,000
Japan	$4,047	Turkey	$3,000
Jordan	$2,428	UK	$7,500
Kenya	$5,000	USA	$10,000
Korea	$1,600		

$: US dollars.

pre-IVF cycle recommendations is relative and cannot be anticipated by infertility experts.

As much as infertile couples are highly committed to medical instructions throughout the IVF processes, the success of IVF or LBR remains below their expectations [26] and the determinants of its success are gaining attention. Healthy neonates, twins, triplets or even those born with congenital defects or other complications are accounted as live birth outcomes. Miscarriages or stillbirth are accounted as failures, but not usually presented as an outcome measure for infertility clinics. The LBR after IVF has been presented in various forms in literature such as the LBR per couple-cycle, the conditional LBR at a specific cycle and the cumulative LBR. The LBR per couple-cycle is calculated by dividing the total number of live neonates obtained by the couple over the total number of IVF cycles that this couple underwent since their commencement of IVF treatment at the same infertility clinic multiplied by 100 [27]. The mean of live births per patient-cycle is then computed. The live birth at a specific cycle (conditional probability) is calculated by dividing the number of live neonates at a specific IVF cycle (first, second, etc.) over the number of couples who received this specific cycle within a certain time frame [28]. The cumulative LBR (conservative estimate) is calculated by dividing the number of live neonates up to and including a specific IVF cycle over the number of couples who had received these IVF cycles [28-30]. Another LBR calculation method assumes that couples who did not return for subsequent IVF cycles had the same chance of a live birth as those who did return for treatment. It is often referred to as the optimistic cumulative LBR, as many couples will not return after a poor response to an infertility treatment [27]. This method may overestimate the cumulative LBR [27]. On the other hand, a conservative cumulative LBR assumes that couples who did not return for subsequent IVF cycles had no chance of a pregnancy resulting in a live birth. Therefore, a population's cumulative LBR probably lies between these two estimates [28].

Lower LBRs have been reported among couples complaining of unexplained or idiopathic infertility [8]. Although infertility treatment modalities follow standard management protocols, such as lifestyle modifications, operative laparoscopy, gonadotropins with intra-uterine insemination, and IVF (with or without intra-cytoplasmic sperm injection), the optimal treatment strategy is always in favor of candidates with clear clinical diagnoses [8]. Secondary infertile couples who had at least one previous incidence of normal pregnancy are expected to have higher LBRs than those with primary infertility. The difference between the male and female infertility factor is often present too (Table 1). The number of causes and factors contributing to female infertility exceeds that of male infertility [31], and semen analysis is accounted as a rapid/

early assessment in any infertility investigation [10].

The consecutive IVF cycles often play a role in the success or failure of IVF treatment. For instance, a decrease in pregnancy rates was reported among couples who underwent more than four IVF cycles [32]. This decline was similar to a nationwide study conducted in the United States [28]. Some studies cited stress, lack of treatment success, and the financial burdens as the major reasons for treatment failures and discontinuation [33-35]. The cumulative LBR in one free service center ranged between 54.8% and 67.1% for up to three cycles [29]. Consecutive IVF cycles are known to run in parallel with additional diagnostic tests conducted by the clinicians that aid in further exploring a more accurate etiology of the disease and resolving it as early as possible. The frequency of trials probably urges couples to increase their compliance with the pre-cycle recommended lifestyle modifications. Therefore, the factor of multiple trials and time always favor higher chances of success and that is why presenting the LBRs per specific cycle and cumulative rates is a more reflective measure of IVF outcomes.

Performance Indicator or a Researched Science

Divisions of reproductive medicine often perceive the LBR as the single most important performance indicator for any infertility clinic, but it does not necessarily signify the quality of service. Infertility clinics all over the world implement quality management systems to aid in monitoring their treatment efficiency and outcomes. In fact, accrediting bodies mandate the presence of a quality-controlled and patient-centered system [36]. The quality of laboratory equipment, consumables, work stations and design all may influence the success rate of IVFs. Quality management not only enhances the medical treatment of infertility, but also boosts the financial performance and increases the customer satisfaction [37]. However, despite having a well-established quality management system, infertility experts should also take into account the couple and disease characteristics as determinants of LBR that vary in their degree of association. One study stated that due to these numerous potential determinants of success, it can be challenging for infertility experts to predict individualized chances of success for each couple. In other words, a clinical prediction model that estimates the LBR before IVF is of great interest for any couple in their counseling stage, yet it does not exist [38]. In addition, the compliance of couples with the standardized pre-cycle counseling package, as well as the etiology of infertility all influences such outcomes and should be considered too. One meta-analysis study concluded that IVF candidates generally comply with IVF counseling packages for the first three cycles, and that this compliance is more likely to increase the success rate by 15%. This study also recommended from national registries to monitor and track such compliance [39]. Reporting the positive IVF outcomes in terms of success or LBRs rather than failures to conceive are more appealing for the public. Infertility experts are advised to present the LBR at their settings in one of the three methods reported in literature and should be aware of their features. Continuous efforts should be paid to investigate further associated variables with infertility and measure the compliance of infertile couples prior to IVF cycles.

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Conflict of Interest

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Abbreviations

LBR: live birth rate; IVF: *in vitro* fertilization

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