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Factors influencing successful pregnancy outcomes in IVF cycles among Jordanian infertile couples

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Summary

Objective: To analyze different factors influencing positive pregnancy rate (PPR) and live birth rates (LBR) following in vitro fertilization (IVF). *Materials and Methods:* Between January 2009 and December 2015, a total of 1,451 embryo transfer (ET) cycles were performed at the Fertility Unit at Jordan University Hospital. Only the first fresh cycles (1,025) were included. Data were collected from the unit registry. *Results:* PPR was achieved in 44.3% (n=454) of cycles, while live birth rate was 36.9% (n=378). PPR and LBR in women younger than 35 years of age was 47.5% and 33.5, respectively. In women aged 35-39 years, PPR was 27.6% while LBR was 15.6%, and for women older than 40 years PPR and LBR, it was 10.9% and 4.7%, respectively. Causes of infertility did not affect PPR or LBR. The maximum percentage of live birth was achieved when 11-15 oocytes were retrieved (39.4%) and when three embryos were transferred (36.9%). Live birth rate was not affected significantly by the number of embryos transferred. *Conclusion:* Women's age is the main determinant of live birth rate after IVF. Cause of infertility did not affect live birth rate.

Key words: In vitro fertilization; Age; Infertility; Live birth rate; Positive pregnancy rate; Jordan.

Introduction

In vitro fertilization (IVF) was first reported as a treatment option for women with severe tubal disease [1, 2]. With improved efficacy after the introduction of gonadotropin stimulation and intracytoplasmic sperm injection (ICSI) [3], indications for IVF have expanded to include severe male-factor infertility, severe endometriosis, ovulatory dysfunction, diminished ovarian reserve, and infertility of unexplained cause [1, 4-6].

IVF has also become an effective treatment option for couples wishing to undergo pre-implantation genetic diagnosis or screening [7, 8], and for those wishing to freeze their oocytes or embryos for preservation of fertility [9-13]. This has been reflected in the rapid expansion of indications for IVF and an estimated 1.5-2 million IVF cycles are being performed annually worldwide [14-16].

Abnormal semen parameters may be a contributing factor in up to 40% of infertile couples [17]. In cases of severe oligospermia (fewer than five million motile sperm/ml), severe asthenospermia (less than 5% progressive motility), and severe teratospermia (less than 4% normal morphology based on strict Kruger criteria), IVF, or a combination of IVF and ICSI, should be offered [5, 18].

Female factors account for 50% of infertility cases worldwide [14]. Tubal-factor infertility accounts for 30% of cases of female infertility [19]. The incidence of endometriosis is reported to be in the range of 9-50% among women who underwent laparoscopy for infertility evaluation [20]. Ovulatory dysfunction is a very common cause of female infertility, accounting for 25% of cases. In this category, polycystic ovary syndrome (PCOS) is the most common cause of anovulation [21]. Other causes include hypogonadotrophic hypogonadism and other endocrinopathies such as thyroid disorders and hyperprolactinaemia [14].

Unexplained infertility is defined as the absence of an identifiable cause of infertility, despite a thorough investigation demonstrating tubal patency, normal semen parameters, ovulation, normal ovarian reserve, and a normal endometrial cavity [22]. The incidence of unexplained infertility ranges from 10-30% [23].

Previous studies have shown no significant effect of infertility etiologies on the success of IVF. Pregnancy chances were determined by female age, duration of infertility and previous pregnancy [10, 24, 25]. Other factors where studied such as body mass index (BMI), ethnicity, and duration of embryo transfer (ET) [18, 26].

The first IVF baby was born in Jordan in May 1987 [27]. Many Jordanian fertility units introduce the latest technologies related to assisted reproduction; this coupled with excellent success rates led to Jordan being a major attraction for patients from neighboring countries with fertility

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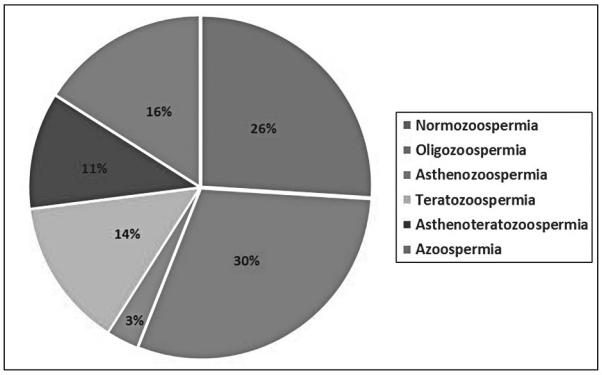

Figure 1. — Distribution of the men included in the study sample according to their seminal fluid analysis.

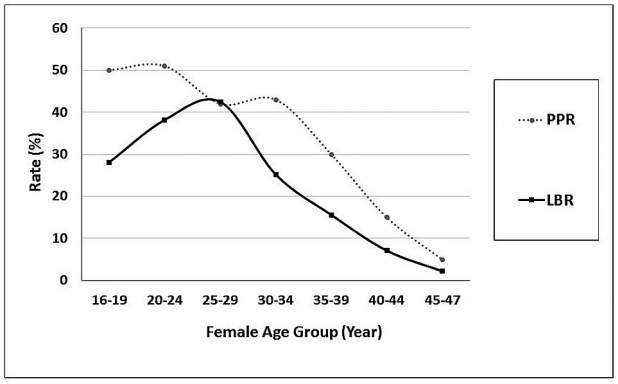

Figure 2. — Rate of positive pregnancy and live birth rates in terms of female age (n=454).

issues [16, 28]. Although great advances have been made in the field of assisted reproductive technology (ART) in Jordan in terms of the number of ART units, available treatment technologies, and pregnancy outcomes, until this day there is no agency [similar to UK Human Fertilization and Embryology Authority (HFEA)] that collects data on all licensed fertility clinics.

Worldwide, several studies have been published discussing factors affecting IVF success rate [10, 24, 25, 29, 30]. Previous studies showed that LBR differs between different ethnic subgroups, which might be attributed to different genetic background, life style, and cultural factors [26, 31-33]. Yet and according to the present authors' knowledge, no studies from Jordan assessed factors influencing successful outcomes of IVF.

This study aimed at evaluating factors influencing pregnancy outcomes among Jordanian women undergoing IVF in the Fertility Unit at Jordan University Hospital. The authors believe that their findings will be useful to help council couples about their realistic probabilities of success of IVF.

Materials and Methods

This study was performed at the Fertility Unit at Jordan University Hospital, Amman, Jordan. Patients' data were obtained from patient's registry at the unit. Between January 2009 and December 2015, a total of 1,451 ET cycles were performed. From those ET cycles, only 1,025 cycles were included where women were undergoing their first, fresh ICSI cycles. Restricting the analysis to first cycles enabled the authors to report rates of failure per individual woman. Information regarding the age of the couples, cause of infertility, seminal fluid analysis data, previous pregnancy (primary *vs.* secondary infertility), number of oocytes retrieved, fertilization rate, number of embryos transferred, and outcomes of pregnancy (biochemical, ectopic, miscarriage or live birth) were collected. Unfortunately, information about BMI or duration of infertility was not available. File and computerized records were reviewed by two different persons.

The study was approved by the Institute Review Board (IRB) of Jordan University Hospital and the Deanship of Academic Research at the University of Jordan (962/2016/19).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), Version 20.0. Descriptive statistics were presented as numbers, percentages, and means ± standard deviations. The Z-test and the difference between proportions test were used to test the difference in proportions and the Student's *t*-test and ANOVA were used for continuous data. All statistical analysis was performed at $p < 0.05$ level of significance.

Results

A total of 1,025 infertile couples were included in the current study. The characteristics of the participating couples are shown in Table 1. The cause of infertility in almost one-third (35%) of the cases was due to the male partner, 33% due to a female factor, both partners (combined) were responsible for 11% of the infertility cases, and in 21% of the cases the cause was idiopathic (unexplained infertility). The female infertility included tubal factor (40%), anovulation (39%), endometriosis (6%), and others such as uterine fibroids and congenital uterine abnormalities (15%).

Semen parameters for men included in the current study were normal (WHO, 2010) in 26% of couples. Semen parameters abnormalities included: azoospermia in 16% of couples, where fertilization was achieved using ICSI with surgically retrieved spermatozoa from microsurgical testicular sperm extraction, oligospermia (fewer than five million sperm/ml), and different abnormalities in morphology and/or motility (Figure 1).

The main outcome measure was live birth per ET (LBR; LBR). Results were also analyzed for positive pregnancy test done on day 14 per ET performed. Evidence of conception was based on positive hCG (> 20 IU). Pregnancy test was positive in 44.3% of the couples. Positive pregnancy rate (PPR) and LBR in women younger than 35 years of age was 47.5% and 33.5, respectively. In women aged 35-39 years, PPR was 27.6% while LBR was 15.6%, and for women older than 40 years PPR and LBR was 10.9% and 4.7%, respectively. The highest rate of positive preg-

Table 1. — *Clinical characteristics of the study sample. Data are presented as percentage and mean ± standard deviation.*

Factor	Value
Male age (years)	38.2 ± 8.0
Female age (years)	32.3 ± 6.3
Primary infertility	69.0% (n=707)
Secondary infertility	31.0% (n=318)
Cause of infertility	
- Male	35.0%
- Female	33.0%
- Combined	11.0%
- Unexplained	21.0%
Number of oocytes retrieved	7.2 ± 5.1
Number of transferred embryos	3.0 ± 1.2
Fertilization rate	78.0% (n=378)
Positive pregnancy rate	44.3% (n=454)
Live birth rate	36.9% (n=800)

Table 2. — *Clinical characteristics of the study sample by result of pregnancy test. a: p < 0.05.*

Pregnancy test	Negative	Positive
Female age (years)	33.2 ± 6.5	30.3 ± 5.5[a]
Cause of infertility		
Male factor	31.9%	33.4%
Female factor	35.7%	30.8%
- Tubal	47.9%	41.2%
- Anovulation	32.4%	41.5%
- Endometriosis	4.7%	6.1%
- Other	15.0%	11.2%
Combined	9.7%	11.2%
Unexplained	22.7%	24.6%
Number of oocytes retrieved	7.3 ± 5.0	6.9 ± 5.3
Fertilization rate	70.0%	89.1%[a]
Number of embryos transferred	3.1 ± 1.0	2.9 ± 1.3

Table 3. — *Clinical characteristics of the study sample by IVF outcome. a: p < 0.05.*

IVF outcome	Failed IVF (no live birth)	Live birth
Female age (years)	33.1 ± 6.2[a]	29.7 ± 5.1
Cause of infertility		
Male factor	27.9%	34.9%
Female factor	33.3%	30.7%
- Tubal	57.6%	40.1%
- Anovulation	25.1%	42.1%
- Endometriosis	4.5%	2.0%
- Other	*12.5%*	*15.8%*
Combined	13.4%	11.5%
Unexplained	25.4%	22.9%
Number of oocytes retrieved	6.1 ± 2.7	8.4 ± 5.1
Fertilization rate	70.3%	75.0%
Number of embryos transferred	3.1 ± 1.0	3.0 ± 1.0

nancy test (51%) was in the age group 20-24 years (Figure 2). Yet, the highest rate of live birth (42.5%) was in the age group 25-29 years (Figure 2). There was a sharp decline in both PPR and LBR in women older than 35 years.

Female age was the main factor that affected both of PPR and LBRs (Tables 2-4). Infertility etiologies did not have a significant effect ($p > 0.05$) on PPR or LBR (Tables 2, 3). The average number of oocytes retrieved did not have a significant effect ($p > 0.05$) on PPR or LBR (Table 5). Women with less than three oocytes retrieved had the lowest PPR and LBR (Table 5). PPR and LBR increased with the increasing number of oocytes up to 15 and declined beyond 15 oocytes (Table 5). Women who had a positive pregnancy test had statistically significant ($p < 0.05$) higher fertilization rate (Table 2), however, it was not different among women who achieved a live birth.

PPR increased when three embryos were transferred as compared to one or two embryos (Table 6). This percentage declined slightly when four embryos were transferred; however, this decline was not significant (as compared to three embryos). On the other hand, the rate of live birth was not affected significantly ($p > 0.05$) by the number of embryos transferred (Table 6).

The participating couples were also classified based on pregnancy outcomes [failed IVF (biochemical, miscarriage, ectopic) or live birth] (Table 4). Female age was the only significant factor in achieving a live birth (Table 4). Infertility etiologies did not have any effect ($p > 0.05$) on the outcomes of pregnancy (Table 4). Biochemical pregnancy was reported in 3.4% of women with positive pregnancy test, ectopic pregnancy in 1.9%, and miscarriage in 11.4%. Live birth was achieved in 83 percent of women with positive pregnancy test.

Discussion

To the [present authors' knowledge, this study is the first to look at predictors of IVF success rate among Jordanian women undergoing IVF and perhaps the region [34-37]. Comprehensive reproductive history, infertility causes, ovarian reserve, gonadotropin dose, and embryo quality are important factors to predict LBR in women undergoing IVF [25, 38].

This study clearly shows that age of women seeking infertility treatments a major factor influencing IVF outcome. The mean age of women included in the current study was 32.3 years. Although the figure seems relatively high for a Middle Eastern country, it is not surprising for Jordan in which the trend is towards an increase in the age of marriage for both men and women; more focus is given to education and career [39]. Teenage pregnancy is rare in Jordan. In 1990, 7% of women aged 15-19 years had given birth; the figure decreased to 4% in 1998 and to 0% in 2012 [39, 40].

The decline in female fertility is gradual over her repro-

Table 4. — Classification of the study sample according to pregnancy outcomes.

Pregnancy outcome	Biochemical n=15	Ectopic n=9	Miscarriage n=52	Live Birth n=378
Female age (years)	35.0 ± 6.8[b]	32.3 ± 6.2[a]	32.1 ± 5.7[a]	29.7 ± 5.1
Cause of infertility				
Male factor	23.4%	24.2%	36.1%	34.9%
Female factor	41.6%	27.3%	31.1%	30.7%
- Tubal	60.5%	71.4%	40.9%	40.1%
- Anovulation	29.8%	8.6%	37.8%	42.1%
- Endometriosis	3.1%	9.4%	1.0%	2.0%
- Other	6.6%	10.6%	20.3%	15.8%
Combined	12.8%	17.3%	10.1%	11.5%
Unexplained	22.2%	31.2%	22.7%	22.9%
Number of eggs retrieved	6.1 ± 2.7	6.3 ± 2.4	7.9 ± 4.5	8.4 ± 5.1
Fertilization rate	68.0%	74.0%	9.0%	75.0%
Number of embryos transferred	3.0 ± 0.8	3.3 ± 1.1	3.1 ± 1.0	3.0 ± 1.0

a: p< 0.05; b: p < 0.01 between live birth and other groups.

Table 5. — *The effect of number of oocytes retrieved on positive pregnancy rate and live birth rate.*

Number of oocytes retrieved	Positive pregnancy rate	*p*-value	Live birth rate	*p*-value
< 3	22.1%	-	16.8%	-
3-6	34.4%	*<0.05	32.9%	*<0.05
		**<0.05		**<0.01
7-10	42.2%	*<0.05	35.2%	*<0.05
		**<0.01		**<0.05
11-15	52.7%	*<0.05	39.4%	*<0.05
> 15	40.3%	*<0.001	30.7%	*<0.05
		**<0.05		**<0.05

**between <3 oocytes retrieved and other groups; **between 11-15 oocytes retrieved and other groups.*

Table 6. — *The effect of number embryos transferred on positive pregnancy rate and live birth rate.*

Number of embryos transferred	Positive pregnancy rate	*p*-value	Live birth rate	*p*-value
1	21.5%	-	18.4%	-
2	27.1%	*>0.05	25.8%	*>0.05
3	48.4%	*<0.001	36.9%	*>0.05
		**<0.001		**>0.05
4	44.9%	*<0.001	32.6%	*>0.05
		**<0.001		**>0.05

**p < 0.001 between 1 transferred embryo and other groups; **p < 0.001 between two transferred embryos and other groups.*

ductive life. Female fertility is reduced on average by 6% for females aged 25-29 years [41], reaching 31% for females aged 35-39 years, with a much greater decease thereafter [42]. In the current study, the highest percentage of positive pregnancy test was recorded in women aged 20-24 years, meanwhile the highest rate of live birth was reported in women aged 25-29. The percentage for both dropped dramatically after the age of 35 years. Previous studies have shown that LBR was highest in women aged 25-30 years, with poorer outcomes in older women [43].

Advanced maternal age is associated with a decline in the number of oocytes retrieved, embryos available for transfer, and embryo quality [44, 45]. This ultimately results in lower implantation, pregnancy, and LBRs [44]. A strong correlation also exists between advanced maternal age and the incidence of chromosomal anomalies. The risk of miscarriage approaches 50% among women over the age of 40 years [46].

The current study did not show that infertility etiology affected PPR or LBR. The extent to which the underlying etiology itself can influence in vitro success rate has been the subject of considerable study. Initial reports indicated certain causes of infertility to be associated with a lower chance of success than others. However, large published studies on the effect of the cause of infertility have shown no significant effect on outcome of IVF [18, 47].

Success rate in IVF is correlated with the number of oocytes retrieved. Regardless the woman's age, success rate is low when less than three oocytes are retrieved [48]. Women under the age of 37 years have good LBRs when three to six oocytes are retrieved, and the rates increase when the number is more than six [49, 50]. The current study showed that the number of oocytes to maximize percentage of positive pregnancy test and LBR is 11-15 oocytes. Researchers also reported that there is no difference in LBR when retrieving more than ten oocytes as compared to six to nine oocytes [51]. In the present study, LBR increased with an increasing number of oocytes up to 15, which was in accordance with previous studies [49-51].

Other factors that affect LBRs are the number and quality of embryos transferred [38, 52]. PPR and LBR increased when three embryos were transferred compared to one or two embryos, and declined when four embryos were transferred. In the early days of IVF, the main goal of IVF treatment was to maximize pregnancy rates. It was shown that the pregnancy rate was related to the number of embryos transferred [53]. Despite both a statistically and clinically higher PPR and LBR, multiple ET is known to be associ-

ated with high multiple pregnancy rates.

Nowadays, with the increased effectiveness of ART, there is growing evidence worldwide towards single ET and thereby decreasing the incidence of multiple pregnancies and its complications, without compromising the chances of pregnancy [53-56].

It is worth mentioning that from the nine cases of ectopic pregnancies, 71% (six cases) were associated with tubal disease. Unfortunately, the number of cases did not allow the authors to show any statistical or clinical significance. The effect of tubal damage or dysfunction on IVF outcome is controversial [57, 58]. Although tubal disease in general is not associated with poor IVF outcome, there is increasing evidence that distal tubal disease is associated with hydrosalpinx, which may affect the chances of success from IVF treatment [59-61]. While a number of early clinical factors were considered in the present study, the authors were unable to examine the effects of BMI, lifestyle characteristics, such as smoking, alcohol intake, and caffeine consumption

Conclusion

Given the relationship between advanced maternal age and the decline in fertility in terms of ovarian reserve, it is not surprising that maternal age is the most important determining factor of success in women undergoing IVF. The increasing tendency to delay childbearing for career, social, or other reasons is putting women under great pressure. Women at risk of premature ovarian failure owing to gonadotoxic chemotherapy or radiation treatment should be offered the possibility of fertility preservation. Women with family history of premature ovarian failure may also benefit from fertility preservation. Cryopreservation of embryos is widely used in Jordan. It is a recognized option for female fertility preservation for couples. On the other hand, other fertility-preservation procedures, such as cryopreservation of oocytes and ovarian tissues are not yet widely adopted. Increasing awareness among women and physicians about these options is of paramount importance to preserve future fertility chances.

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