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Impact of governmental support to the IVF outcome: differences between public and private clinical settings. A prospective cohort study.

Running title: **Utilization of governmental support of IVF procedures**

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Abstract

Objectives

Infertility rates have been increasing in low- and middle-income countries, including Kazakhstan. Need for accessible and affordable assisted reproductive technologies become essential for many subfertile women. This study aimed to explore whether public funding is associated with less psychological distress for women undergoing in-vitro fertilization (IVF) treatment, whether public funding and clinical setting are independently associated with IVF outcomes, and whether publicly funded women have different IVF success rates depending on the type of clinical setting.

Design

A prospective cohort study

Setting

Three private and two public IVF clinics in Kazakhstan

Participants

Women aged ≥ 18 who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English.

Primary and secondary outcome measures

The primary outcome was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks.

Results

Patients attending private clinics and women who self-paid for IVF treatment had higher depression, infertility-related stress, and anxiety scale scores than women who attended public clinics and publicly funded, respectively. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), and transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$), and had statistically significantly higher pregnancy rate compared to public clinics (79.0% vs 29.7%, $p<0.001$). Risks of the clinical pregnancy were lower among patients who attended public clinics and who self-paid for IVF treatment multiple regression models after adjusting for covariates. Regardless of clinical settings, public funding was associated with higher pregnancy rates.

Conclusions

Further expansion of public funding for IVF services is necessary to decrease psychological pressure associated with financial burden among subfertile women. It is advised to strengthen IVF public clinics while allowing more public funding allocated to private clinics.

Key words: Governmental support, financial support, utilization, Infertility; IVF treatment; Stress; Depression; Anxiety; Kazakhstan

Strengths and limitations of this study

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings.

Non-response bias may result in underestimation the association between the IVF outcome and baseline psychological status because it is possible that those who refused to participate had poor prognosis and were likely depressed and distressed.

22% of the study participants had unknown IVF outcomes and were excluded from multivariable analysis.

Although we controlled for several covariates in the models, an inclusion of additional variables such as behavioral, environmental factors, parental demographical characteristics, embryo quality, and experience and qualification of physicians could benefit future research in obtaining less biased results.

Introduction

Infertility is defined as inability to conceive within 12 months of unprotected sexual intercourse in women younger than 35 years or within 6 months in women older than 35 years.[1 2] Infertility affects a significant proportion of the population around the globe, and it is estimated to affect between 8 and 12% of reproductive-aged couples worldwide. [3-5] However, in some developing countries, the rates of infertility are much higher, reaching 25-30% in some populations.[3 6] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[7] Taking in consideration that the desire of parenthood is one of the basic human needs and rights, the worldwide problem with infertility becomes even more dramatic. In most societies, despite of the cultural or religious preferences, becoming a parent is perceived as an essential component in achieving self-realization and meaning in life.[8]

According to studies, women undergoing IVF treatment usually experience stress and anxiety.[9] Although psychological factors have potential and considerable impact on in vitro fertilization (IVF) outcome, their precise relationship needs further detailed investigations as existing literature data remains inconclusive.[9-11] The consequences of infertility and subsequent childlessness are much more depressive in developing countries when compared with high-income states due to sociocultural differences and accessibility to infertility treatment.[4]

From the other side, there is a huge demand and unmet need for assisted reproductive technologies (ART), especially in developing countries with the high rate of infertility.[6] A health economic report in 2002 put the lowest estimate of global need for ART at 1500 cycles per million populations per year, assuming that only 50% of couples who need ART will have it done.[6] At the same time, there is a large difference in both infertility services availability and quality between high- and low-income countries and between the rich and the poor in the same country,[6] particularly in ART procedures, which violates the basic ethical principles of justice, equity and equality.[6] Despite an increasing medical demand for infertility treatments, public funding challenges for IVF exist in many developing countries.[12] While high-income countries like France, Spain, and Israel, provide full coverage of IVF treatments as a part of social policy, low-income countries cannot afford it. In the situation when coverage for IVF is absent or incomplete, it makes the IVF treatments unaffordable to couples with the most need. From both the public health and economic standpoint, financial support of IVF may represent a good investment in terms of governmental financial returns, even in lower-income countries with state-financed health care systems such as Ukraine, Belarus, and Kazakhstan.[12] There are at least two specific interest to support IVF treatments from a governmental perspective: (1) a long-term financial benefits from citizens' meeting the basic needs of parenthood and (2) creating new citizens who will eventually become future taxpayers. However, access to IVF is dependent not only on the particular country income but also on the efficiency of wealth distribution, and the health policy, and health insurance system.[6 12]

Kazakhstan is a developing Central Asian republic, and one of the countries with the highest regional prevalence of infertility.[3 12-15] Fertility as a corner-stone of a family planning in Central Asian culture plays an important role in the strength of couples' relationship.[15] However, the fertility rate in Kazakhstan decreased significantly from 4.6 in 1960 to 2.8 in 2015,[14] and the prevalence of infertility varies from 12 to 15.5%.[13-15] Considering the infertility issue in Kazakhstan, the need for accessible and affordable assisted reproductive technologies (ART) is found to be very high.

A pioneer clinic for in vitro fertilization (IVF) in Kazakhstan was established in 1995 with the first newborn delivered in 1996. Since 2010 the Ministry of Healthcare provides funds for IVF coverage and few public IVF clinics have been established. Although the funds are limited in amount, for the period of 2010-2018 with the governmental support (quotas), around 3000 babies were born with IVF procedure facilitation. According to the Kazakhstani State Program, in 2021 the government will fund 7000 IVF cycles.[16] It is 7-times more than in 2020 (1000 cycles). Considering the mentioned circumstances, it is very important to investigate factors that might have an impact on the IVF outcome, and to understand how effectively governmental money has been utilized.

The aims of the study were (1) to assess presence of infertility-related stress, anxiety, and depressive symptoms among patients undergoing IVF procedure; (2) to evaluate the relationships between psychological factors and clinical settings (public and private), as well as, between psychological factors and IVF treatment payment type (governmental paid and self-paid); (3) to assess the associations of IVF outcomes with psychological factors, clinical setting and payment type; and (4) to examine whether the association between payment type and IVF outcomes was modified by clinical setting.

Methods

Study design

This prospective cohort study was conducted among women attending ART clinics between June 2019 and September 2020 in Kazakhstan. Women seeking first or repeated IVF treatment were asked to participate in the study, providing them with oral and written informed consent. The response rate was 14% (446 out of 3223). Adult women who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Women who were under 18 years old, who were not able to answer the survey questions in Kazakh, Russian or English languages and who refused to provide written informed consent were excluded. The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee (#120/28012019).

The study participants were enrolled from three private and two public ART clinics. All private clinics located in major cities are branches of one for-profit medical organization. This private organization was established in 1995 and performed the first IVF treatment in Kazakhstan. The public clinics were also from major cities – the National Research Center of Mother and Child Health (NRCMCH) in Nur-Sultan city and the Regional Perinatal Center in Aktobe city. The hospital-based public clinics have started providing ART treatment since 2007 and 2018, respectively. NRCMCH was accredited and certified according to the Joint Commission International standards.

Study variables

The binary outcome variable was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. Patients provided socio-demographic and baseline psychological status data through a survey and validated scales, respectively. Additional independent variables - clinical history data, IVF past and present data – were extracted from patients' medical records. A full description of the variables appears elsewhere.[15]

The psychological status was measured in relation to depression, stress, and anxiety. Depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D) developed by Radloff.[17] In this study, the Cronbach's alpha coefficient for CES-D scale was 0.92. To measure levels of infertility stress, the Fertility Problem Inventory (FPI) was utilized.[18] FPI assesses five different aspects of infertility-related stress: social concerns, sexual concerns, relationship concerns, rejection of childfree lifestyle and need for parenthood. Combining all FPI subscales contribute to global infertility stress score with the maximum score 276, indicating the highest level of infertility-related stress. In this study, the Cronbach's alpha coefficient for FPI global infertility stress scale was 0.85. Lastly, Anxiety level was measured with Spielberger State-Trait Anxiety Inventory (STAI).[19] First 10 items in the scale assess state anxiety (STAI State) – transitory feelings of apprehension, dread and tension accompanied with physiological arousal, whereas the last 10 items measure trait anxiety (STAI Trait) – individual differences in responding to a stressful situation with intensified state anxiety. The high scores in the scales correspond to severity of anxiety. In this study, the Cronbach's alpha coefficients for STAI-S and STAI-T subscales were 0.90 and 0.84, respectively. All scales were translated in Russian and Kazakh languages by experienced researchers and then back translated to check appropriateness to the original versions. Correlation coefficients among the scales ranged from 0.17 to 0.27 (except r=0.73 between STAI-S and STAI-T) indicating appropriate differentiation of depression, stress and anxiety from each other.

Statistical analysis

In descriptive analysis, continuous variables were summarized as means or medians and corresponding variability measurements (standard deviations and inter-quartile ranges). Categorical variables were described in frequencies and percentages. To compare means between two-groups, independent t-test or Mann-Whitney U-test was used, where appropriate. To test an independence between two categorical variables, chi-square test or Fisher's exact test was performed. To test intercorrelations between FPI, CES-D, STAI-S and STAI-T scales, Person's correlation coefficients were calculated. Simple and multiple Poisson regression modeling with robust estimation were implemented to assess relationships of independent variables with the outcome variable. Additionally, linear regression models were constructed to test associations of independent variables with the number of oocytes retrieved, since the number of oocytes retrieved is considered a strong predictor for the clinical pregnancy.[20 21] Models were built according to the parsimonious principle, including reasonable number of covariates based on their clinical, epidemiological importance and statistical significance. We hypothesized that the payment type and clinical setting would be highly associated, and inclusion both of them would result in multicollinearity. However, no multicollinearity was observed. To check multicollinearity, we utilized variance inflation factor and examined changes in coefficients and its standard errors by adding in and removing these variables from the models. It was decided to include both variables in the regression modeling as private clinics look for additional income by treating publicly funded patients, likewise public clinics are encouraged to provide out-of-pocket services. No interaction was observed between payment type and clinical setting at significance level 0.05. Also models were stratified to private and public clinics.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Four hundred forty-six women attending IVF clinics agreed to participate in the study. The average age of the participants was 33.8±5.6 years (Table 1). One third of women was overweight or obese (27.9%), approximately half of them had education level at ISCED 6 (45.1%), and two thirds paid themselves (out-of-pocket) for IVF treatment (67.9%). On average, infertility duration was 5.9±3.9 years (Table 2). A female factor as a cause of infertility was determined in a half of the women, while in others factor was mixed or male, and a quarter of the women had previously attempted at least one IVF cycle treatment (24.2%). Most women were treated with short or long classic protocol, and pregnancy rate reached 62.2% (Table 3).

Table 1. Socio-demographic characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Age (years), mean±SD	33.8±5.6	33.9±4.9	33.7±5.9	0.81
Missing data=2%				
BMI, n(%)				
Underweight	44 (11.0)	10 (7.3%)	34 (12.9%)	<0.01
Normal	245 (61.1)	76 (55.5%)	169 (64.0%)	
Overweight/Obese	112 (27.9)	51 (37.2%)	61 (23.1%)	
Missing data=10%				
Education level, n(%)				
ISCED 4	120 (27.0%)	51 (36.4%)	69 (22.7%)	<0.01
ISCED 5	124 (27.9%)	26 (18.6%)	98 (32.2%)	
ISCED 6	200 (45.1%)	63 (45.0%)	137 (45.1%)	
Missing data=0.5%				
Location, n(%)				
Aktobe	67 (15.0%)	67 (47.2%)	0 (0%)	
Almaty	99 (22.2%)	0 (0%)	99 (32.6%)	
Nur-Sultan	183 (41.0%)	75 (52.8%)	108 (35.5%)	
Shymkent	97 (21.8%)	0 (0%)	97 (31.9%)	
Missing data=0%				
Payment type, n(%)				
State-funded	112 (32.1%)	85 (59.9%)	27 (13.0%)	<0.001
Self-paid	237 (67.9%)	57 (40.1%)	180 (87.0%)	
Missing data=21.8%				

Table 2. Past IVF medical history of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Comorbidity, n(%)				
Yes	174 (39.0%)	83 (58.4%)	91 (29.9%)	<0.001
No	272 (61.0%)	59 (41.6%)	213 (70.1%)	
Missing data=0%				
Infertility duration (years)				
Mean±SD	5.9±3.9	6.0±3.5	5.9±4.1	0.75
Median (IQR)	5 (3-8)	6 (3-8)	5 (3-8)	
Missing data=5.6%				
Number of previous deliveries, n(%)				
None	298 (67.1%)	106 (74.6%)	192 (63.6%)	<0.001
One	112 (25.2%)	36 (25.4%)	76 (25.2%)	
2 or more	34 (7.7%)	0 (0%)	34 (11.2%)	
Missing data=0.5%				
Number of previous miscarriages, n(%)				
None	384 (86.5%)	127 (89.4%)	257 (85.1%)	0.21
One or more	60 (13.5%)	15 (10.6%)	45 (14.9%)	
Missing data=0.5%				
Number of previous intentional pregnancy interruptions, n(%)				
None	404 (91.0%)	125 (88.0%)	279 (92.4%)	0.14
One or more	40 (9.0%)	17 (12.0%)	23 (7.6%)	
Missing data=0.5%				
Number of previous IVF cycles, n(%)				
None	335 (75.8%)	106 (75.2%)	229 (76.1%)	0.41
One	67 (15.2%)	25 (17.7%)	42 (13.9%)	
2 or more	40 (9.0%)	10 (7.1%)	30 (10.0%)	
Missing data=0.9%				
Cause of infertility, n(%)				
Female	218 (49.3%)	57 (40.4%)	161 (53.5%)	<0.01
Male	41 (9.3%)	8 (5.7%)	33 (11.0%)	
Mixed	183 (41.4%)	76 (53.9%)	107 (35.5%)	
Missing data=0.9%				

Table 3. Clinical IVF characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Number of oocytes retrieved				
Mean±SD	1.5±2.0	8.1±7.2	11.5±8.4	<0.001
Median (IQR)	1 (0-2)			
Missing data=9%				
Number of embryos transferred				
Mean±SD	2.0±2.2	1.4±1.1	2.2±2.5	<0.001
Median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	
Missing data=14.8%				
Used protocol				
Classic-long	36 (8.3%)	5 (3.7%)	31 (10.3%)	0.06
Classic-short	379 (86.9%)	122 (90.4%)	257 (85.4%)	
Non-classic – natural cycle	7 (1.6%)	2 (1.5%)	5 (1.7%)	
Non-classic – ultrashort	13 (3.0%)	5 (3.75)	8 (2.7%)	
Non-classic – stimulated in luteal phase	1 (0.2%)	1 (0.7%)	0 (0%)	
Missing data=2.2%				
Clinical pregnancy, n (%)				
Yes	216 (62.2%)	35 (29.7%)	181 (79.0%)	<0.001
No	131 (37.8%)	83 (70.3%)	48 (21.0%)	
Missing data=22.2%				
Clinical pregnancy rate per number of embryos transferred, %	38.3	22.0	44.7	<0.01

Public vs private clinics.

More than two thirds of women attended private clinics (68.2%). There were no differences in age ($p=0.81$), infertility duration ($p=0.75$), number of previous miscarriages ($p=0.21$), number of previous intentional pregnancy interruptions (0.14), number of previous IVF cycles ($p=0.41$) between participants of public and private clinics (Table 2). The public clinics had statistically significantly higher proportions of overweight or obese women ($p<0.01$), patients with education level at ISCED 4 ($p<0.01$) and patients who were publicly funded ($p<0.001$) than the private clinics. The proportion of patients with comorbidities was also higher in the public clinics (58.4% vs 29.9%, $p<0.001$) than in the private clinics. However, the percentage of women with history of previous deliveries ($p<0.001$) and the proportion of patients who had a female factor as a cause of infertility ($p<0.01$) were statistically significantly higher among patients in the private clinics. The private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), and transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$) than the public clinics (Table 3). Private clinics had statistically significantly higher pregnancy rate compared to the public clinics (79.0% vs 29.7%, $p<0.001$).

Most women were at risk for clinical depression (74.6%, Table 4). Patients attending private clinics had, on average, higher depression score than women in the public clinics (25.2 vs 18.3, $p<0.001$) and over four-fifths of patients in the private clinics were at risk for clinical depression. Infertility-related stress scores in social concern, sexual concern, relationship concern and global stress subscales were statistically significantly higher among women in the private clinics. In addition, patients in the private clinics had, on average, higher anxiety scale scores than women who attended the public clinics. In comparison to publicly funded patients, self-paid patients had statistically significantly higher depression scale score, infertility-related stress (social concern, sexual concern and relationship concern) score and anxiety scale scores (Table 4).

Table 4. Depression, stress, and anxiety levels between public and private clinics; and between publicly funded and self-paid IVF patients.

Scales	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	All, N=446 (100%)	Publicly funded, n=112 (32.1%)	Self-paid, n=237 (67.9%)
CES-D score, mean±SD	18.3±9.6	25.2±10.0***	22.9±10.4	19.3±9.7	24.3±11.4***
Categorized CES-D score, n (%)					
No risk for clinical depression (< 16)	58 (40.9%)	48 (17.4%)***	106 (25.4%)	69 (61.6%)	177 (74.7%)*
At risk for clinical depression (≥ 16)	84 (59.1%)	228 (82.6%)	312 (74.6%)	43 (38.4%)	60 (25.3%)
Missing data=6.3%					
FPI scale					
Social concern, mean±SD	29.5±6.6	33.3±5.6***	32.0±6.2	30.5±6.8	32.4±6.1*
Sexual concern, mean±SD	20.4±6.8	25.7±6.0***	23.9±6.8	20.9±7.0	24.4±6.7***
Relationship concern, mean±SD	28.0±6.6	32.7±7.2***	31.1±7.3	28.1±7.4	31.8±7.5***
Need for parenthood, mean±SD	43.5±9.1	41.7±7.3*	31.7±7.5	43.0±8.6	42.6±8.1
Rejection of childfree lifestyle, mean±SD	32.0±6.2	31.5±8.0	42.3±8.0	31.8±6.7	32.8±8.3
Global stress, mean±SD	153.3±18.4	164.9±21.8***	160.9±21.4	154.3±20.5	163.9±23.3***
Missing data=7.4%					
STAI State, mean±SD	41.9±11.4	47.1±9.7***	45.3±10.6	42.0±11.1	44.5±10.0*
STAI Trait, mean±SD	44.1±8.4	48.8±7.5***	47.1±8.1	44.8±8.3	47.2±8.1*
Missing data=9%					

*p<0.05, **p<0.01, ***p<0.001

Factors associated with IVF outcomes.

In bivariable analysis, clinical pregnancy was statistically significantly associated with BMI, education level, location, type of payment, history of comorbidity, number of previous IVF cycles and number of oocytes retrieved during IVF treatment (Supplementary Tables 1-3). In simple Poisson regression analysis with robust estimation, higher CES-D score was positively associated (RPR=1.01, 95% 1.00-1.02) with successful clinical pregnancy, as a large proportion of pregnant women were at risk for clinical depression ($p<0.01$, Supplementary Table 4). However, after adjusting for age, BMI, education, payment type, clinical setting, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of oocytes retrieved and number of embryos transferred, CES-D score was not anymore associated with clinical pregnancy (Table 5). In bivariable analysis, no differences were observed between pregnant and non-pregnant women in terms of FPI scale scores (except rejection of childfree lifestyle, $p<0.001$), and anxiety scale scores (Supplementary Table 4). After controlling for the above-mentioned covariates, higher FPI global stress score and higher STAI State score were independently associated with reduced pregnancy rates (Table 5).

Table 5. Simple and multiple Poisson and linear regression analyses of psychological factors, clinical settings and payment type predicting IVF clinical pregnancy and number of oocytes retrieved.

Scales	Clinical pregnancy		Number of oocytes retrieved	
	Crude RR (95% CI)	[&]Adjusted RR (95% CI)	Crude β-coefficient (95% CI)	†Adjusted β-coefficient (95% CI)
		Model 1		**Model 5**
CES-D score	1.01 (1.00-1.02)*	1.00 (0.99-1.01)	-0.04 (-0.12; 0.04)	-0.04 (-0.12; 0.05)
Public clinics	0.38 (0.28-0.50)*	0.39 (0.29-0.53)*	-3.43 (-5.13; -1.72)*	-5.86 (-8.10; -3.61)*
Self-paid	1.23 (0.99-1.52)	0.81 (0.67-0.97)*	0.16 (-1.73; 2.04)	-3.20 (-5.42; -0.98)*
		Model 2		**Model 6**
FPI scale: Global stress score	0.99 (0.99-1.00)	0.99 (0.990-0.997)*	0.01 (-0.04; 0.04)	0.01 (-0.03; 0.05)
Public clinics	-	0.38 (0.28-0.51)*	-	-5.39 (-7.52; -3.25)*
Self-paid	-	0.85 (0.70-1.03)	-	-3.53 (-5.65; -1.40)*
		Model 3		**Model 7**
STAI State	0.99 (0.99-1.01)	0.99 (0.984-0.999)*	-0.06 (-0.13; 0.02)	-0.02 (-0.11; 0.07)
Public clinics	-	0.38 (0.28-0.51)*	-	-5.71 (-7.92; -3.51)*
Self-paid	-	0.81 (0.67-0.98)*	-	-3.33 (-5.57; -1.09)*
		Model 4		**Model 8**
STAI Trait	1.00 (0.99-1.02)	0.99 (0.98-1.00)	-0.11 (-0.21; -0.01)*	-0.07 (-0.18; 0.04)
Public clinics	-	0.38 (0.28-0.52)*	-	-5.92 (-8.14; -3.69)*
Self-paid	-	0.81 (0.67-0.98)*	-	-3.27 (-5.50; -1.03)*

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.
† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles
*$p<0.05$

IVF procedures in public clinics were negatively associated with the clinical pregnancy in simple and all multiple Poisson regression models (Table 5). Those who self-paid for IVF cycles had statistically significantly lower clinical pregnancy rates than those who were funded by the state in all multiple regression models. In the stratified analysis, self-payment was also independently associated with lower clinical pregnancy rates in private clinics, whereas in public clinics the same tendency was observed, however, with no statistical significance (Table 6).

Table 6. Multiple Poisson regression models stratified by private and public clinics investigating associations IVF clinical pregnancy with psychological factors and payment type.

Scales	Private clinics &Adjusted RR (95% CI)	Public clinics &Adjusted RR (95% CI)
	Model A	**Model B**
CES-D score	1.00 (0.99-1.01)	1.00 (0.97-1.04)
Self-paid	0.80 (0.68-0.95)*	0.60 (0.33-1.12)
	Model C	**Model D**
FPI scale: Global stress score	0.99 (0.98-0.99)*	1.00 (0.98-1.01)
Self-paid	0.86 (0.73-1.02)	0.60 (0.33-1.09)
	Model E	**Model F**
STAI State	0.99 (0.986-0.998)*	0.97 (0.94-0.99)*
Self-paid	0.78 (0.66-0.93)*	0.77 (0.41-1.43)
	Model G	**Model H**
STAI Trait	0.99 (0.99-1.00)	0.94 (0.88-1.00)
Self-paid	0.80 (0.67-0.95)*	0.70 (0.36-1.38)

& Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

None of psychological scale scores were associated with the number of oocytes retrieved during IVF treatment (Table 5). On average, statistically significantly lower number of oocytes were retrieved in public clinics and among those who self-paid IVF cycles in all multiple linear regression models (Table 5).

Discussion

This is the first multicenter study conducted comparing IVF outcomes between private and public clinics in Kazakhstan. The study results show that the private clinics had a substantially higher pregnancy rate. This difference could be partially explained by the more rigorous selection of subfertile women with better IVF prognosis in private clinics. Indeed, our study results confirm it: the private clinics had a lower percentage of overweight or obese women and lower proportion of women with comorbidities than public clinics. Previous studies have shown that higher BMI levels and infertility-related comorbidities were negatively predictive of IVF outcomes.[20 22] In addition, the private clinics retrieved and transferred statistically significantly higher number of oocytes and embryos, respectively. Systematic review and meta-analysis by Van Loendersloot et al illustrated that higher number of oocytes retrieved, and number of embryos transferred were positively associated with successful IVF outcomes.[20] As treatment costs per an IVF cycle are high, patients in private clinics want to maximize likelihood to conceive a child by retrieving and transferring more oocytes and embryos in a given IVF cycle.[23] However, transferring more embryos is associated with multiple pregnancies.[24] Introduction of insurance coverage or public funding of reproductive treatment in many countries has resulted in the reduction of the number of embryos transferred per cycle, consequently, decreased incidence rates of multiple pregnancies.[23 25 26]

After controlling for potential confounding variables, patients in private clinics still were more likely to conceive a child than patients in public clinics. Independent from the number of oocytes retrieved and number of embryos transferred, the private clinics had higher clinical pregnancy rates. To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 5). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[15] The sensitivity analysis revealed that the private clinics still were independently associated with higher clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates.

Given that we controlled for important confounding variables in the models, lower pregnancy rates in public clinics could be attributed to other factors. First, availability of state funding increases the utilization of IVF services and proportionally increases the number of women with poor reproductive prognosis.[27] Patients with worse prognosis are unlikely to seek IVF treatment if the insurance or state coverage is not provided for all who need. Second, while patients with better prognosis remain in long waiting lists in public clinics, they undergo their first IVF cycles in private clinics. Thus, patients with higher likelihood of conceiving a child are treated in private clinics whereas public clinics treat patients with worse prognosis and longer infertility duration as they remain in the long waiting lists.[28] Third, patients with higher socio-economic status are likely to choose private clinics. Previous studies have shown that patients from poor socio-economic communities had lower levels of anti-Mullerian hormone and antral follicle count, indicating reduced ovarian reserve and a lower probability of conceiving a child.[29] Fourth, private clinics are likely to recruit and retain, with better salary offers and benefits, more skillful and experienced physicians who are able to retrieve sufficient quantity and quality of oocytes and to perform successful embryo transfer procedures. Several studies have suggested that a "physician factor" is an important predictor of successful IVF outcomes[30] align with the number of oocytes retrieved,[31] number of high-quality embryos transferred and absence of blood or mucus on the transfer catheter.[32] The results of the linear regression models showed that public clinics, on average, retrieved a low number of oocytes (Table 5). This finding support two explanations listed above. Low oocytes retrieval in public clinics could indicate higher proportions of patients with poor prognosis (reduced ovarian reserve) or less skillfulness and experience of physicians working in public clinics who are able to retrieve an adequate quantity and quality eggs.

Also, our study results indicate that self-payment was negatively associated with the clinical pregnancy in the multiple regression models. We hypothesized that women who self-paid would have different IVF outcomes depending on clinical settings. To test this hypothesis, regression models were built by stratifying to public and private clinics (Table 6). However, regardless of the clinical settings women who self-paid had worse IVF outcomes than publicly funded women. Observed non-significant estimates of self-payment in the public clinics could be explained by a small sample size in this stratum.

Based on previous studies, we expected that publicly funded women would have a lower pregnancy rate than women who self-paid because public funding eliminates barriers related to treatment costs and encourages women with worse prognosis to seek IVF treatment.[23 25 26] However, public funding is not widely available in Kazakhstan – only a small percentage of subfertile women receive funding. Those who are selected to receive state funding usually have a higher probability of conceiving a child.[33] Bureaucratic barriers, in addition, discourage financially disadvantaged patients from applying for public funding and seeking IVF treatment. While financially independent patients who do not meet public funding criteria – because of their worse reproductive prognosis – seek IVF treatment by paying out-of-pocket. This speculation is supported by the findings from the multiple linear regression modeling factors associated with the number of oocytes retrieved (Table 5). In the linear model, independent from other factors, patients who self-paid had lower number of oocytes retrieved, indicating reduced ovarian reserve, thus, lower probability to become pregnant.[21]

The study results showed that before starting IVF treatment a large percentage of women were at risk of clinical depression. State and trait anxiety levels at baseline, also, were substantially higher among IVF patients than the general population. Similarly, the high prevalence of depression and high anxiety levels among IVF patients were reported by previous research.[34-36] It was suggested that pre-treatment major depressive disorder (MDD) is associated with MDD during IVF treatment which could have a potential negative impact on IVF outcomes.[35] Likewise, high stress and anxiety levels at baseline do not change over time during IVF treatment.[36] Notably, women attending private clinics, prior to IVF procedures, were more likely depressed, experience fertility-related stress, and anxiety than women in the public clinics. Similarly, self-paid patients were likely depressed, experience infertility-related stress, and anxiety than publicly funded patients. Since most patients in the private clinics paid out of pocket, they feel psychological pressure to conceive a child because following IVF cycles would put more financial burden on them and decrease their chances to get pregnant.

The multiple regression analyses showed that baseline state anxiety and stress were associated with lower clinical pregnancy rates. Our results are consistent with a systematic review and meta-analysis conducted by Purewal et al and Matthiesen et al.[37,38] Previous studies found associations of lower pregnancy rates with high levels of stress hormones.[39,40] In contrast to a suggestion that the association between negative life events with IVF outcomes is mediated via number of oocytes retrieved,[41] we found stress was independently associated with the clinical pregnancy while adjusting for number of oocytes retrieved. In addition, we did not find association between psychological factors and number of oocytes retrieved.

Strengths and limitations

This is the first multicenter study investigating potential predictors for the IVF outcomes between different clinical settings. The multivariable analysis that included clinically and epidemiologically important variables in the models allowed to examine independent relationships of the clinical settings, payment type, and psychological factors with the clinical pregnancy rates. In addition, sensitivity analysis provided more robust results in drawing conclusions.

There are also several study limitations that should be mentioned. Firstly, non-response bias could be present as the response rate was very low (14%). Since descriptive data on non-respondents were not collected for comparison, we were not able to confirm or exclude non-response bias. The non-response bias may result in underestimation the association between the IVF outcome and baseline psychological status because it is possible that those who refused to participate had poor prognosis and were likely depressed and distressed. Regarding clinical setting, the response rates were similar – 13% for public and 15% for private clinics. Thus, it is unlikely that low response rate attenuated the association between the clinical setting and the IVF outcome. Overall, given low response rate, the generalisability of the study results should be considered with caution. Secondly, data on IVF outcomes were unknown for 22% of the study participants. The associations of the IVF outcomes with poor prognosis predictors could be underestimated, as women with unknown IVF outcomes had poor prognosis (were likely overweight or obese, had longest infertility duration and higher proportion of those who previously attempted IVF cycles) and were not included in the multivariable analysis.[42] Thirdly, other important variables that could potentially affect IVF outcomes were not collected. Although we controlled for several covariates in the models, an inclusion of additional variables (behavioral factors – smoking, alcohol consumption, physical activity; environmental factors; parental demographical characteristics; embryo quality; experience and qualification of physicians) could benefit future research in obtaining less biased results. Another limitation is that depression, anxiety, and stress levels were only measured at baseline. Repeated measurements at different time points could provide a clear picture of the relationships between psychological factors with IVF outcomes because these factors tend to fluctuate over IVF treatment time. Lastly, a small sample size in the stratified analysis did not allow to obtain more robust estimates of the effect sizes of the independent variables on the pregnancy rates.

Conclusions

The study results illustrate high prevalence of depression and anxiety among IVF patients than the general population. We also found that higher stress and anxiety levels were negatively associated with the clinical pregnancy. Patients who attended private clinics and those who paid out-of-pocket experience higher psychological distress related to additional financial burden, in case of unsuccessful IVF outcome. Regardless of clinical settings, public funding was associated with the higher success rate, as patients with better prognosis were selected for the treatment. Independent from payment type, private clinics had better pregnancy rates than public clinics. There is a need to further investigate whether the increase in public funding would influence overall IVF success rate and decrease psychological distress associated with financial pressure among subfertile women.

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Contributors

GB and MT conceived the study. AI and MT contributed to the study design. GA, ST, TU, SB, AA, GU, ZD, GBe, and AB contributed to the acquisition of data. AI, MT, and GA contributed to data analysis and have verified the underlying data. AI, GA, and ST contributed to the initial drafting of the manuscript. GA, GB, TU, SB, AB, and MT contributed to study supervision. AI, GA, and MT contributed to reviewing and finalizing the manuscript. All authors approved the final version of the report and agree to be accountable for all aspects of the work.

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Competing interests

SB is a paid employee of Ecomed.

Patient consent for publication

Not required.

Ethical approval

The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee and Nazarbayev University Institutional Research Ethics Committee.

Data availability statement

Data can be requested from the corresponding author.

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Supplementary Tables

Supplementary Table 1. Socio-demographic characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Age (years), mean±SD	33.7±5.9	34.5±5.2	0.21	33.0
BMI, n(%)				
Underweight	38 (18.2%)	4 (3.2%)	<0.001	2 (3.0%)
Normal	130 (62.2%)	74 (58.7%)		41 (62.1%)
Overweight/Obese	41 (19.6%)	48 (38.1%)		23 (34.9%)
Education level, n(%)				
ISCED 4	49 (38.0%)	40 (18.5%)	<0.001	31 (31.3%)
ISCED 5	30 (23.3%)	81 (37.5%)		13 (13.1%)
ISCED 6	50 (38.7%)	95 (44.0%)		55 (55.6%)
Location, n(%)				
Aktobe	31 (23.7%)	26 (12.0%)	0.02	10 (10.1%)
Almaty	38 (29.0%)	59 (27.3%)		2 (2.0%)
Nur-Sultan	54 (41.2%)	112 (51.9%)		17 (17.2%)
Shymkent	8 (6.1%)	19 (8.8%)		70 (70.7%)
Type of payment, n(%)				
State-funded	51 (25.9%)	45 (36.6%)	0.04	16 (55.2%)
Self-paid	146 (74.1%)	78 (63.4%)		13 (44.8%)

Supplementary Table 2. Past and current medical history of infertility among the study participants.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Comorbidity, n(%)				
Yes	76 (35.2%)	80 (61.1%)	<0.001	18 (18.2%)
No	140 (64.8%)	51 (38.9%)		81 (81.8%)
Infertility duration (years)				
Mean±SD	5.4±3.7	6.1±4.0	0.13	6.7±3.9
Median (IQR)	4.8 (3-7)	5 (3-8)		6.5 (4-9)
Number of previous deliveries, n(%)				
None	144 (66.7%)	90 (69.2%)	0.29	64 (65.3%)
One	50 (23.1%)	33 (25.4%)		29 (29.6%)
Two or more	22 (10.2%)	7 (5.4%)		5 (5.1%)
Number of previous miscarriages, n(%)				
None	190 (88.0%)	111 (85.4%)	0.49	83 (84.7%)
One or more	26 (12.0%)	19 (14.6%)		15 (15.3%)
Number of previous intentional pregnancy interruptions, n(%)				
None	198 (91.7%)	116 (89.2%)	0.45	90 (91.8%)
One or more	18 (8.3%)	14 (10.8%)		8 (8.2%)
Number of previous IVF cycles, n(%)				
None	179 (83.4%)	90 (68.7%)	<0.01	66 (68.7%)
One	18 (8.4%)	26 (19.8%)		23 (24.0%)
2 or more	18 (8.4%)	15 (11.5%)		7 (7.3%)
Cause of infertility, n(%)				
Female	97 (45.1%)	55 (42.3%)	0.32	66 (68.0%)
Male	16 (7.4%)	16 (12.3%)		9 (9.3%)
Mixed	102 (47.4%)	59 (45.4%)		22 (22.7%)

Supplementary Table 3. IVF treatment characteristics of the study participants.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Number of oocytes retrieved				
Mean±SD	11.2±7.8	8.5±7.9	<0.01	11.6±9.4
Median (IQR)	10 (6-14)	7 (2-13)		6 (4-17)
Number of embryos transferred				
Mean±SD	1.7±0.8	1.7±1.9	0.10	4.7±4.9
Median (IQR)	2 (1-2)	1 (1-2)		2 (1-6.5)
Used protocol, n(%)				
Classic-long	23 (10.7%)	11 (8.4%)	0.27	2 (2.2%)
Classic-short	177 (82.3%)	114 (87.0%)		88 (97.8%)
Non-classic – natural cycle	4 (1.9%)	3 (2.3%)		0 (0%)
Non-classic – ultrashort	11 (5.1%)	2 (1.5%)		0 (0%)
Non-classic – stimulated in luteal phase	0 (0%)	1 (0.8%)		0 (0%)

Supplementary Table 4. Depression, stress and anxiety scales' scores between pregnant and not pregnant women.

Scales	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
CES-D score, mean±SD	24.6±10.3	20.4±11.7	<0.001	22.1±7.1
Categorized CES-D score, n (%)				
No risk for clinical depression (< 16)	45 (21.0%)	49 (38.0%)	<0.01	12 (16%)
At risk for clinical depression (≥ 16)	169 (79.0%)	80 (62.0%)		63 (84%)
FPI scale				
Social concern, mean±SD	32.3±6.1	31.5±6.9	0.27	31.9±5.1
Sexual concern, mean±SD	23.7±6.5	23.5±7.2	0.80	24.9±6.6
Relationship concern, mean±SD	30.8±7.8	31.1±7.0	0.73	31.8±6.5
Need for parenthood, mean±SD	41.9±7.9	43.5±8.8	0.09	41.4±6.5
Rejection of childfree lifestyle, mean±SD	31.1±7.5	34±7.8	<0.001	29.4±5.4
Global stress, mean±SD	159.8±21.2	163.6±24.7	0.13	159.4±14.7
STAI State, mean±SD	44.7±10.2	45.1±10.7	0.74	47.2±11.4
STAI Trait, mean±SD	47.5±7.6	46.6±9.0	0.33	47.2±7.8

Supplementary Table 5. Simple and multiple Poisson regression analyses of psychological factors, clinical settings and payment type predicting IVF clinical pregnancy (sensitivity analysis, excluding women from Astana private clinic (n=108) with the highest pregnancy rate).

Scales	**Clinical pregnancy**	
	Crude RR (95% CI)	**[&]Adjusted RR (95% CI)**
		Model 9
CES-D score	1.02 (1.01-1.03)*	1.01 (0.99-1.02)
Public clinics	0.47 (0.35-0.64)*	0.47 (0.29-0.77)*
Self-paid	1.25 (0.88-1.77)	0.69 (0.43-1.10)
		Model 10
FPI scale: Global stress score	1.00 (0.99-1.01)	0.99 (0.98-0.99)*
Public clinics	-	0.32 (0.19-0.56)*
Self-paid	-	0.67 (0.41-1.10)
		Model 11
STAI State	1.00 (0.99-1.01)	0.99 (0.97-1.00)
Public clinics	-	0.42 (0.26-0.67)*
Self-paid	-	0.72 (0.45-1.16)
		Model 12
STAI Trait	1.02 (0.99-1.03)	1.01 (0.98-1.03)
Public clinics	-	0.45 (0.28-0.71)*
Self-paid	-	0.69 (0.43-1.12)

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl. Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

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Impact of governmental support to the IVF outcome: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

Running title: **Utilization of governmental support of IVF procedures**

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Abstract

Objectives

Infertility rates have been increasing in low- and middle-income countries, including Kazakhstan. Need for accessible and affordable assisted reproductive technologies become essential for many subfertile women. This study aimed to explore whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type.

Design

A prospective cohort study

Setting

Three private and two public IVF clinics located in major cities

Participants

Women aged ≥ 18 seeking first or repeated IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Participants completed a survey on demographical and past medical history data, while clinical data were collected from medical records.

Primary and secondary outcome measures

Clinical pregnancy defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks.

Results

Out of 446 women who participated in the study, 68.2% attended private clinics. Two-thirds of women (59.9%) attending public clinics and 13% of women attending private clinics were publicly funded. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), and transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$), and had a statistically significantly higher pregnancy rate compared to public clinics (79.0% vs 29.7%, $p<0.001$). Women who were publicly funded had on average a higher number of oocytes retrieved and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95%CI 1.02; 1.47) than those who were self-paid in the multiple regression models. No statistically significant interaction between clinical setting and payment type was observed.

Conclusions

Private clinics and public funding were independently associated with higher IVF success rates. There is also a need to further investigate whether the increase in public funding would influence the overall IVF success rate.

Key words: Governmental support, financial support, utilization, Infertility; IVF treatment; Stress; Depression; Anxiety; Kazakhstan

Strengths and limitations of this study

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings.

Non-response bias may result in underestimation the association between the IVF outcome and baseline psychological status because it is possible that those who refused to participate had poor prognosis and were likely depressed and distressed.

22% of the study participants had unknown IVF outcomes and were excluded from multivariable analysis.

Although we controlled for several covariates in the models, an inclusion of additional variables such as behavioral, environmental factors, parental demographical characteristics, embryo quality, and experience and qualification of physicians could benefit future research in obtaining less biased results.

Introduction

Infertility is defined as inability to conceive within 12 months of unprotected sexual intercourse in women younger than 35 years or within 6 months in women older than 35 years.[1 2] Infertility affects a significant proportion of the population around the globe, and it is estimated to affect between 8 and 12% of reproductive-aged couples worldwide. [3-5] However, in some developing countries, the rates of infertility are much higher, reaching 25-30% in some populations.[3] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[6] Taking in consideration that the desire of parenthood is one of the basic human needs and rights, the worldwide problem with infertility becomes even more dramatic. In most societies, despite of the cultural or religious preferences, becoming a parent is perceived as an essential component in achieving self-realization and meaning in life.[7]

One of the most important issues in contemporary assisted reproductive technologies (ART) markets is access to the treatment.[8 9] As infertility is a medical condition, and couples with unfavorable fertility characteristics should have equal access to receive medical care, currently in many countries healthcare policymakers are trying to increasing access to ART treatment for patients who cannot afford to pay out of pocket for the treatment.[8] Moreover, the relative cost that patients pay for ART treatment predicts not only the level of access, but also number of embryos transferred.[9] This fact makes the insurance or governmental support very important. There is a huge demand and unmet need for ART, especially in developing countries with the high rate of infertility.[6] A health economic report in 2002 put the lowest estimate of global need for ART at 1500 cycles per million populations per year, assuming that only 50% of couples who need ART will have it done.[10] At the same time, there is a large difference in both infertility services availability and quality between high- and low-income countries and between the rich and the poor in the same country,[11] particularly in ART procedures, which violates the basic ethical principles of justice, equity and equality.[8 11 12] However, some studies showed that insurance support to ART access can lead to a substantial increase in IVF usage in a market, [8] therefore, controlling by specific patient selection is required. This will ensure that the treatment to couples with severe medical needs will be available.

Despite an increasing medical demand for infertility treatments, public funding challenges for IVF exist in many developing countries.[13] While high-income countries like France, Spain, and Israel, provide full coverage of IVF treatments as a part of social policy, low-income countries cannot afford it. In the situation when coverage for IVF is absent or incomplete, it makes the IVF treatments unaffordable to couples with the most need. From both the public health and economic standpoint, financial support of IVF may represent a good investment in terms of governmental financial returns, even in lower-income countries with state-financed health care systems such as Ukraine, Belarus, and Kazakhstan.[13] There is an interest to support IVF treatments from a governmental perspective. After successful IVF treatment, couples with fertility issues create new citizens who will eventually become future taxpayers. However, access to IVF is dependent not only on the particular country income but also on the efficiency of wealth distribution, and the health policy, and health insurance system.[8 13]

Kazakhstan is a developing Central Asian republic, and one of the countries with the highest regional prevalence of infertility.[3 13-16] Fertility as a corner-stone of a family planning in Central Asian culture plays an important role in the strength of couples' relationship.[16] However, the fertility rate in Kazakhstan decreased significantly from 4.6 in 1960 to 2.8 in 2015,[15] and the prevalence of infertility varies from 12 to 15.5%.[14-16] Considering the infertility issue in Kazakhstan, the need for accessible and affordable assisted reproductive technologies (ART) is found to be very high.

A pioneer clinic for in vitro fertilization (IVF) in Kazakhstan was established in 1995 with the first newborn delivered in 1996. The first ART clinic was private, and before 2010 all expenses for IVF treatment had been paid by patients. Since 2010 the Ministry of Healthcare provides funds for IVF coverage and few public IVF clinics have been established. Apart of public IVF clinics, the public funded IVF cycles are performed in the private clinics as well. Although the funds are limited in amount, for the period of 2010-2018 with the governmental support (quotas), around 3000 babies were born with IVF procedure facilitation. According to the Kazakhstani State Program, in 2021 the government will fund 7000 IVF cycles.[17] It is 7-times more than in 2020 (1000 cycles). Considering the mentioned circumstances, it is very important to investigate factors that might have an impact on the IVF outcome, and to understand how effectively governmental money has been utilized.

We aimed in this study to investigate whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type.

Methods

Study design

This prospective cohort study was conducted among women attending ART clinics between June 2019 and September 2020 in Kazakhstan. Women seeking first or repeated IVF treatment were asked to participate in the study, providing them with oral and written informed consent. The response rate was 14% (446 out of 3223). Adult women who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Women who were under 18 years old, who were not able to answer the survey questions in Kazakh, Russian or English languages and who refused to provide written informed consent were excluded. The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee (#120/28012019).

The study participants were enrolled from three private and two public ART clinics. All private clinics located in major cities are branches of one for-profit medical organization. This private organization was established since 1995 and performed the first IVF treatment in Kazakhstan. The public clinics were also from major cities – the National Research Center of Mother and Child Health (NRCMCH) in Nur-Sultan city and the Regional Perinatal Center in Aktobe city. The hospital-based public clinics have started providing ART treatment since 2007 and 2018, respectively. NRCMCH was accredited and certified according to the Joint Commission

International standards. Both private and public clinics entitled to provide services paid out-of-pocket and under public funding.

IVF treatment is funded through public funding or self-payment (out-of-pocket). Subfertile patients could receive public funding for one IVF cycle per year within the State Guaranteed Health Benefits package of Republic of Kazakhstan. To receive public funding, women must satisfy several inclusion criteria such as being Kazakhstani residents, being in the age range of 18-42 years old, having good ovarian reserve, no severe comorbidities that could substantially reduce a probability of conceiving a child via IVF and no children. Women with ovarian or cervical benign or malignant tumors, acute inflammatory diseases, somatic or psychological diseases, and low ovarian reserve do not fall under the government support. Only 15 clinics, five public and ten private, are accredited to provide IVF services under public funding. On the other hand, self-paid women are not restricted in age, number of IVF cycles per year or clinical setting where undergo IVF treatment. For self-paid women, costs associated with IVF treatment range between US$1,200 – US$3,600 per one IVF cycle.

Study variables

The binary outcome variable was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. Patients with "unknown" status were those who have not yet reached 8 weeks gestation and have not yet had an ultrasound to determine the presence or absence of a clinical pregnancy. Patients provided socio-demographic data such as age in years, body mass index (BMI), education level and payment type (publicly funded or self-paid) through a survey. BMI was categorized as underweight (less than 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and overweight/obese (25 kg/m^2 and above). According to International Standard Classification of Education (ISCED), education level was grouped to ISCED 4 level—secondary high school, ISCED 5 level—post-secondary non-tertiary education and ISCED 6 level—bachelor or master level education). Patients' past medical history data such as all comorbidities associated with infertility, duration of infertility, number of previous deliveries, number of previous miscarriages, number of intentional pregnancy interruptions and number of previous IVF cycles were collected using a standardized survey. Clinical data about the number of oocytes retrieved, number of embryos transferred, cause of infertility (female, male and mixed), type of treatment protocol, and multiple pregnancy were collected from patients' medical records.

Statistical analysis

In descriptive analysis, continuous variables were summarized as means or medians and corresponding variability measurements (standard deviations and inter-quartile ranges). Categorical variables were described in absolute and relative frequencies. To compare means between two-groups, independent t-test or Mann-Whitney U-test was used, where appropriate. To test an independence between two categorical variables, chi-square test or Fisher's exact test was performed. Simple and multiple Poisson regression modeling with robust estimation were implemented to assess relationships of independent variables with the outcome variable. Additionally, linear regression models were constructed to test associations of independent variables with the number of oocytes retrieved, since the number of oocytes retrieved is considered a strong predictor for the clinical pregnancy.[18 19] Models were built according to the parsimonious principle, including reasonable number of covariates based on their clinical, epidemiological importance and statistical significance. We hypothesized that the payment type and clinical setting would be highly associated, and inclusion both of them would result in multicollinearity. However, no multicollinearity was observed. To check multicollinearity, we utilized variance inflation factor and examined changes in coefficients and its standard errors by adding in and removing these variables from the models. It was decided to include both variables in the regression modeling as private clinics look for additional income by treating publicly funded patients, likewise public clinics are encouraged to provide out-of-pocket services. No interaction was observed between payment type and clinical setting at significance level 0.05. Anyway, we presented results from the model with interaction between clinical setting and payment type, as it was practically important to see whether the outcomes differ between private and public clinics depending on payment type. Additionally, we checked for existence of other interactions. The interaction between comorbidity and clinical setting was found statistically significant. Lastly, we examined goodness-of-fit of the final models using Pearson's and deviance goodness of fit tests. The goodness-of-fit statistics were non-significant indicating that the models fitted well enough the sample data.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Four hundred forty-six women attending IVF clinics agreed to participate in the study. The average age of the participants was 33.8±5.6 years (Table 1). One third of women was overweight or obese (27.9%), approximately half of them had education level at ISCED 6 (45.1%), and two thirds paid themselves (out-of-pocket) for IVF treatment (67.9%). On average, infertility duration was 5.9±3.9 years (Table 2). A female factor as a cause of infertility was determined in a half of the women, while in others factor was mixed or male, and a quarter of the women had previously attempted at least one IVF cycle treatment (24.2%). Most women were treated with short or long classic protocol, and cumulative pregnancy rate reached 62.2% (Table 3).

Table 1. Socio-demographic characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Age (years), mean±SD	33.8±5.6	33.9±4.9	33.7±5.9	0.81
Missing data=2%				
BMI, n(%)				
Underweight	44 (11.0)	10 (7.3%)	34 (12.9%)	<0.01
Normal	245 (61.1)	76 (55.5%)	169 (64.0%)	
Overweight/Obese	112 (27.9)	51 (37.2%)	61 (23.1%)	
Missing data=10%				
Education level, n(%)				
ISCED 4	120 (27.0%)	51 (36.4%)	69 (22.7%)	<0.01
ISCED 5	124 (27.9%)	26 (18.6%)	98 (32.2%)	
ISCED 6	200 (45.1%)	63 (45.0%)	137 (45.1%)	
Missing data=0.5%				
Location, n(%)				
Aktobe	67 (15.0%)	67 (47.2%)	0 (0%)	
Almaty	99 (22.2%)	0 (0%)	99 (32.6%)	

Nur-Sultan	183 (41.0%)	75 (52.8%)	108 (35.5%)	
Shymkent	97 (21.8%)	0 (0%)	97 (31.9%)	
Missing data=0%				
Payment type, n(%)				
Publicly funded	112 (32.1%)	85 (59.9%)	27 (13.0%)	<0.001
Self-paid	237 (67.9%)	57 (40.1%)	180 (87.0%)	
Missing data=21.8%				

Table 2. Past IVF medical history of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Comorbidity, n(%)				
Yes	174 (39.0%)	83 (58.4%)	91 (29.9%)	<0.001
No	272 (61.0%)	59 (41.6%)	213 (70.1%)	
Missing data=0%				
Infertility duration (years)				
Mean±SD	5.9±3.9	6.0±3.5	5.9±4.1	0.75
Median (IQR)	5 (3-8)	6 (3-8)	5 (3-8)	
Missing data=5.6%				
Number of previous deliveries, n(%)				
None	298 (67.1%)	106 (74.6%)	192 (63.6%)	<0.001
One	112 (25.2%)	36 (25.4%)	76 (25.2%)	
2 or more	34 (7.7%)	0 (0%)	34 (11.2%)	
Missing data=0.5%				
Number of previous miscarriages, n(%)				
None	384 (86.5%)	127 (89.4%)	257 (85.1%)	0.21
One or more	60 (13.5%)	15 (10.6%)	45 (14.9%)	
Missing data=0.5%				
Number of previous intentional pregnancy interruptions, n(%)				
None	404 (91.0%)	125 (88.0%)	279 (92.4%)	0.14
One or more	40 (9.0%)	17 (12.0%)	23 (7.6%)	
Missing data=0.5%				
Number of previous IVF cycles, n(%)				
None	335 (75.8%)	106 (75.2%)	229 (76.1%)	0.41
One	67 (15.2%)	25 (17.7%)	42 (13.9%)	
2 or more	40 (9.0%)	10 (7.1%)	30 (10.0%)	
Missing data=0.9%				
Cause of infertility, n(%)				
Female	218 (49.3%)	57 (40.4%)	161 (53.5%)	<0.01
Male	41 (9.3%)	8 (5.7%)	33 (11.0%)	
Mixed	183 (41.4%)	76 (53.9%)	107 (35.5%)	
Missing data=0.9%				

Table 3. Clinical IVF characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Number of oocytes retrieved				
Mean±SD	10.5±2.0	8.1±7.2	11.5±8.4	<0.001
Median (IQR)	1 (0-2)			
Missing data=9%				
Number of embryos transferred				
Mean±SD	2.0±2.2	1.4±1.1	2.2±2.5	<0.001
Median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	
Missing data=14.8%				
Used protocol				
Classic-long	36 (8.3%)	5 (3.7%)	31 (10.3%)	0.06
Classic-short	379 (86.9%)	122 (90.4%)	257 (85.4%)	
Non-classic – natural cycle	7 (1.6%)	2 (1.5%)	5 (1.7%)	
Non-classic – ultrashort	13 (3.0%)	5 (3.75)	8 (2.7%)	
Non-classic – stimulated in luteal phase	1 (0.2%)	1 (0.7%)	0 (0%)	
Missing data=2.2%				
Clinical pregnancy, n (%)				

Yes	216 (62.2%)	35 (29.7%)	181 (79.0%)	<0.001
No	131 (37.8%)	83 (70.3%)	48 (21.0%)	
Missing data=22.2%				
Clinical pregnancy rate per number of embryos transferred, %	38.3	22.0	44.7	<0.01
Multiple pregnancies, n(%)				
Yes	4 (1.0%)	0 (0%)	4 (1.4%)	0.32
No	418 (99.0%)	131 (100%)	287 (98.6%)	
Missing data=5%				

Public vs private clinics.

More than two thirds of women attended private clinics (68.2%). There were no differences in age (p=0.81), infertility duration (p=0.75), number of previous miscarriages (p=0.21), number of previous intentional pregnancy interruptions (0.14), and number of previous IVF cycles (p=0.41) between participants of public and private clinics (Table 2). The public clinics had statistically significantly higher proportions of overweight or obese women (p<0.01), patients with education level at ISCED 4 (p<0.01) and patients who were publicly funded (p<0.001) than the private clinics. The proportion of patients with comorbidities was also higher in the public clinics (58.4% vs 29.9%, p<0.001) than in the private clinics. However, the percentage of women with history of previous deliveries (p<0.001) and the proportion of patients who had a female factor as a cause of infertility (p<0.01) were statistically significantly higher among patients in the private clinics. The private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had more multiple pregnancies (0 vs 4, p=0.32) than the public clinics (Table 3). Private clinics had statistically significantly higher cumulative pregnancy rate compared to the public clinics (79.0% vs 29.7%, p<0.001).

Publicly funded vs self-paid

One third of women (32.1%) received public funding for IVF treatment. There was no difference between publicly funded and self-paid patients in terms of age, BMI, comorbidity, number of previous miscarriages and number of previous intentional pregnancy interruptions (Supplementary Tables 1-2). Despite that the number of oocytes retrieved, number of embryos transferred, and type of treatment protocol used were comparable in the two groups, cumulative clinical pregnancy rates were statistically significantly different between them (53.1% vs 65.2%, p=0.04, publicly funded vs self-paid, respectively, Supplementary Table 3).

Factors associated with IVF outcomes.

In bivariable analysis, clinical pregnancy was statistically significantly associated with BMI, education level, location, type of payment, history of comorbidity, number of previous IVF cycles and number of oocytes retrieved during IVF treatment (Supplementary Tables 4-6).

Table 4 . Simple and multiple Linear and Poisson regression analyses of clinical settings and payment type predicting the number of oocytes retrieved and IVF clinical pregnancy.

	Number of oocytes retrieved	Clinical pregnancy

	Crude β-coefficient (95% CI)	†Adjusted β-coefficient (95% CI)	Crude RR (95% CI)	&Adjusted RR (95% CI)
	Model 1		Model 4	
Public clinics	-3.4 (-5.1; -1.7)	-3.7 (-5.5; 1.9)	0.38 (0.26; 0.54)*	0.44 (0.33; 0.59)*
	Model 2		Model 5	
Public clinics	-3.4 (-5.1; -1.7)	-5.6 (-7.8; -3.4)*	0.38 (0.26; 0.54)*	0.39 (0.29; 0.52)*
Publicly funded	-0.2 (-2.0; 1.7)	3.3 (1.1; 5.5)*	0.82 (0.59; 1.12)	1.23 (1.02; 1.47)*
	Model 3 †Adjusted β-coefficient (95% CI)		Model 6 &Adjusted RR (95% CI)	
	Publicly funded	Self-paid	Publicly funded	Self-paid
Public clinics	-3.31 (-6.81; 0.19)	-6.86 (-9.49; -4.22)*	0.46 (0.33; 0.64)*	0.30 (0.17; 0.54)*

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles

& Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*$p<0.05$

RR = relative risk. CI = confidence interval. The interactions between payment type and clinical setting were not statistically significant in Model 3 and Model 6.

Public clinics on average retrieved lower number of oocytes than private clinics (estimated β-coefficient= -5.6, 95% CI-7.8; -3.4) controlling for payment type and other covariates (Table 4). While adjusting for number of oocytes retrieved, number of embryos transferred and payment type, IVF procedures in public clinics were independently negatively associated with the clinical pregnancy (RR=0.39, 95% CI 0.29; 0.52). Women who were publicly funded for IVF treatment had on average higher number of oocytes retrieved (estimated β-coefficient=3.3, 95% CI 1.1; 5.5) and statistically significantly higher probability of clinical pregnancy (RR=1.23, 95% CI 1.02; 1.47) than those who were self-paid in the multiple regression models.

Even though we did not find statistically significant difference in the estimated effect sizes of clinical setting depending on payment type, we noticed that among self-paid women public clinics had stronger negative association with IVF outcomes (relatively lower number of oocytes retrieved and lower clinical pregnancy rates) than among patients who were publicly funded. There was, additionally, a statistically significant interaction between clinical settings and comorbidity in predicting IVF clinical pregnancy. Adjusted RR of clinical pregnancy between public clinics vs private clinics among patients with no history of comorbidities was 0.72 (0.54; 0.95), while among those with a history of at least one comorbidity was 0.13 (0.07; 0.26) adjusted for age, BMI, education, payment type, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

Discussion

This is the first multicenter study conducted comparing IVF outcomes between private and public clinics in Kazakhstan. The study results show that the private clinics had a substantially higher clinical pregnancy rate. This difference could be partially explained by the more rigorous selection of subfertile women with better IVF prognosis in private clinics. Indeed, our study results confirm it: the private clinics had a lower percentage of overweight or obese women and lower proportion of women with comorbidities than public clinics. Previous studies have shown that higher BMI levels and infertility-related comorbidities were negatively predictive of IVF outcomes.[18 20] In addition, the private clinics retrieved and transferred statistically significantly higher number of oocytes and embryos, respectively. Systematic review and meta-analysis by Van Loendersloot et al illustrated that higher number of oocytes retrieved, and number of embryos transferred were positively associated with successful IVF outcomes.[18] As treatment costs per an IVF cycle are high, patients in private clinics want to maximize likelihood to conceive a child by retrieving and transferring more oocytes and embryos in a given IVF cycle.[21] However, transferring more embryos is associated with multiple pregnancies.[22] Indeed, our study results found that all multiple pregnancies occurred among women attending private clinics. Introduction of insurance coverage or public funding of reproductive treatment in many countries has resulted in the reduction of the number of embryos transferred per cycle, consequently, decreased incidence rates of multiple pregnancies.[21 23 24]

After controlling for potential confounding variables, patients in public clinics still were less likely to conceive a child than patients in private clinics. Independent from the number of oocytes retrieved and number of embryos transferred, public clinics had lower clinical pregnancy rates. To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 7). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[16] The sensitivity analysis revealed that the public clinics still were independently associated with lower clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates.

Given that we controlled for important confounding variables in the models, lower pregnancy rates in public clinics could be attributed to other factors. First, while patients with better prognosis remain in long waiting lists in public clinics, they undergo their first IVF cycles in private clinics. Thus, patients with higher likelihood of conceiving a child are treated in private clinics whereas public clinics treat patients with worse prognosis and longer infertility duration as they remain in the long waiting lists.[25] Second, patients with higher socio-economic status are likely to choose private clinics. Previous studies have shown that patients from poor socio-economic communities had lower levels of anti-Mullerian hormone and antral follicle count, indicating reduced ovarian reserve and a lower probability of conceiving a child.[26] Third, private clinics are likely to recruit and retain, with better salary offers and benefits, more skillful and experienced physicians who are able to retrieve sufficient quantity and quality of oocytes and to perform successful embryo transfer procedures. Several studies have suggested that a “physician factor” is an important predictor of successful IVF outcomes[27] align with the number of oocytes retrieved,[28] number of high-quality embryos transferred and absence of blood or mucus on the transfer catheter.[29] The results of the linear regression models showed that public clinics, on average, retrieved a low number of oocytes (Table 4). This finding support two explanations listed above. Low oocytes retrieval in public clinics could indicate higher proportions of patients with poor prognosis (reduced ovarian reserve) or less skillfulness and experience of physicians working in public clinics who are not able to retrieve an adequate quantity and quality eggs.

Based on previous studies, we expected that publicly funded women would have a lower pregnancy rate than women who self-paid because public funding eliminates barriers related to treatment costs and encourages women with worse prognosis to seek IVF treatment.[21 23 24] However, public funding is not widely available in Kazakhstan and only a small percentage of subfertile women receive funding. Thus, those who are selected to receive state funding usually have a higher probability of conceiving a child.[30] Indeed, our study results showed that publicly funded women had higher likelihood of conceiving a child than self-paid women. Bureaucratic barriers, in addition, discourage financially disadvantaged patients from applying for public funding and seeking IVF treatment. While financially independent patients who do not meet public funding criteria – because of their worse reproductive prognosis – seek IVF treatment by paying out-of-pocket. This speculation is supported by the findings from the multiple linear regression modeling factors associated with the number of oocytes retrieved (Table 4). In the linear model, independent from other factors, patients who were publicly funded had higher number of oocytes retrieved than self-paid women which indicates that self-paid patients had reduced ovarian reserve, thus, lower probability to become pregnant.[19] It is likely that when public funding become more widely available in Kazakhstan, the utilization of IVF services will increase and not only women with better reproductive prognosis will access IVF treatment, but also patients with poor prognosis. Thus, the relative number of women with poor reproductive prognosis is expected to proportionally increase.[31] Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has been shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.[32]

Despite that the interaction between clinical setting and payment type was not statistically significant, we found that among self-paid women public clinics had stronger negative association with IVF outcomes (relatively lower number of oocytes retrieved and lower clinical pregnancy rates) than among women who were publicly funded. There is a need to conduct further studies to investigate existence of the interaction between clinical setting and payment type among IVF patients. Also, we found that patients with a history of at least one comorbidity and attending public clinics had the lowest probability of conceiving a child. It is likely that patients with more severe comorbidities undergo IVF cycles in public clinics because they might have been refused to be treated in private clinics – the more rigorous selection process of subfertile women with better IVF prognosis is in place. Previous studies have shown that medical comorbidities were negatively associated with IVF pregnancy rates.[33 34] However, none of the studies examined the effect modification of medical comorbidities on the relationship between clinical setting and IVF outcomes.

Strengths and limitations

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings. The multivariable analysis that included clinically and epidemiologically important variables in the models allowed to examine independent relationships of the clinical settings and payment type with the IVF outcomes. In addition, sensitivity analysis provided more robust results in drawing conclusions.

There are also several study limitations that should be mentioned. Firstly, non-response bias could be present as the response rate was very low (14%). Since descriptive data on non-respondents were not collected for comparison, we were not able to confirm or exclude non-response bias. Regarding clinical setting, the response rates were similar – 13% for public and 15% for private clinics. Thus, it is unlikely that low response rate attenuated the association between the clinical setting and the IVF outcomes. Overall, given low response rate, the generalizability of the study results should be considered with caution. Secondly, data on IVF outcomes were unknown for 22% of the study participants. The associations of the IVF outcomes with poor prognosis predictors could be underestimated, as women with unknown IVF outcomes had poor prognosis (were likely overweight or obese, had longest infertility duration and higher proportion of those who previously attempted IVF cycles) and were not included in the multivariable analysis.[35] Thirdly, other important variables that could potentially affect IVF outcomes were not collected. Although we controlled for several covariates in the models, an inclusion of additional variables (behavioral factors – smoking, alcohol consumption, physical activity; environmental factors; parental demographical characteristics; embryo quality; experience and qualification of physicians) could benefit future research in obtaining less biased results. Lastly, a small sample size in the regression models did not allow to obtain more robust estimates of the effect sizes of the independent variables and examine other potential interactions among them.

Conclusions

Private clinics and public funding were independently associated with higher IVF success rates. Difference in IVF pregnancy rates between private and public clinics is not only associated with demographical and clinical characteristics of patients, but also could be related to factors-associated with clinical setting. There is also a need to further investigate whether the increase in public funding would influence overall IVF success rate among subfertile women.

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Contributors

GB and MT conceived the study. AI and MT contributed to the study design. GA, ST, TU, SB, AA, GU, ZD, GBe, and AB contributed to the acquisition of data. AI, MT, and GA contributed to data analysis and have verified the underlying data. AI, GA, and ST contributed to the initial drafting of the manuscript. GA, GB, TU, SB, AB, and MT contributed to study supervision. AI, GA, and MT contributed to reviewing and finalizing the manuscript. All authors approved the final version of the report and agree to be accountable for all aspects of the work.

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Competing interests

SB is a paid employee of Ecomed IVF private clinic.

Patient consent for publication

Not required.

Ethics statement

The University Medical Center Institutional Research Ethics Committee(№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee(#120/28012019)

Data availability statement

Data can be requested from the corresponding author.

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Supplementary Tables

Supplementary Table 1. Socio-demographic characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Age (years), mean±SD	34.2±4.8	34.2±5.9	0.99	32.1±5.7
BMI, n(%)				
Underweight	12 (10.8%)	32 (13.9%)	0.62	0 (0%)
Normal	69 (62.2%)	132 (57.1%)		44 (74.6%)
Overweight/Obese	30 (27.0%)	67 (29.0%)		15 (25.4%)
Education level, n(%)				
ISCED 4	39 (34.8%)	47 (20.0%)	<0.01	34 (35.1%)
ISCED 5	27 (24.1%)	90 (38.3%)		7 (7.2%)
ISCED 6	46 (41.1%)	98 (41.7%)		57.7%)
Location, n(%)				
Aktobe	41 (36.6%)	26 (11.0%)	<0.001	0 (0%)
Almaty	3 (2.7%)	96 (40.5%)		0 (0%)
Nur-Sultan	68 (60.7%)	115 (48.5%)		0 (0%)
Shymkent	0 (0%)	0 (0%)		97 (100%)

Supplementary Table 2. Past and current medical history of infertility of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Comorbidity, n(%)				
Yes	49 (43.7%)	125 (52.7%)	0.12	0 (0%)
No	63 (56.3%)	112 (47.3%)		97 (100%)
Infertility duration (years)				
Mean±SD	6.6±3.6	5.1±3.9	<0.01	7.0±3.9
Median (IQR)	6 (4-8)	4 (3-7)		6 (4-9.5)
Number of previous deliveries, n(%)				
None	87 (77.7%)	150 (63.5%)	<0.01	61 (63.5%)
One	24 (21.4%)	62 (26.3%)		26 (27.1%)
Two or more	1 (0.9%)	24 (10.2%)		9 (9.4%)
Number of previous miscarriages, n(%)				
None	100 (89.3%)	205 (86.9%)	0.52	79 (82.3%)
One or more	12 (10.7%)	31 (13.1%)		17 (17.7%)
Number of previous intentional pregnancy interruptions, n(%)				
None	101 (90.2%)	209 (88.6%)	0.65	94 (97.9%)
One or more	11 (9.8%)	27 (11.4%)		2 (2.1%)
Number of previous IVF cycles, n(%)				
None	84 (75.7%)	184 (78.6%)	0.03	67 (69.1%)
One	20 (18.0%)	22 (9.4%)		25 (25.8%)
2 or more	7 (6.3%)	28 (12.0%)		5 (5.1%)
Cause of infertility, n(%)				
Female	35 (31.2%)	106 (45.3%)	<0.01	77 (80.2%)
Male	6 (5.4%)	22 (9.4%)		13 (13.5%)
Mixed	71 (63.4%)	106 (45.3%)		6 (6.3%)

Supplementary Table 3. IVF treatment characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Number of oocytes retrieved				
Mean±SD	10.2±8.0	10.3±8.1	0.87	11.2±8.8
Median (IQR)	9 (4-14)	9 (4-14)		9 (4-14)
Number of embryos transferred				
Mean±SD	1.6±1.0	1.5±0.8	0.93	4.5±4.8
Median (IQR)	2 (1-2)	2 (1-2)		2 (1-6)
Used protocol, n(%)				
Classic-long	7 (6.6%)	28 (12.0%)	0.09	1 (1.0%)
Classic-short	94 (89.5%)	189 (80.8%)		96 (99.0%)
Non-classic – natural cycle	2 (1.9%)	5 (2.1%)		0 (0%)
Non-classic – ultrashort	1 (1.0%)	12 (5.1%		0 (0%)
Non-classic – stimulated in luteal phase	1 (1.0%)	0 (0%)		0 (0%)
Clinical pregnancy, n (%)				
Yes	51 (53.1%)	146 (65.2%)	0.04	19 (70.4%)
No	45 (46.9%)	78 (34.8%)		8 (29.6%)
Miscarriage, n(%)				
Yes	0 (0%)	1 (0.4%)	1.00	0 (0%)
No	102 (100%)	225 (99.6%)		24 (100%)
Multiple pregnancies, n(%)				
Yes	1 (1.0%)	3 (1.3%)	1.00	0 (0%)
No	103 (99.0%)	226 (98.7%)		89 (100%)

Supplementary Table 4. Socio-demographic characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Age (years), mean±SD	33.7±5.9	34.5±5.2	0.21	33.0
BMI, n(%)				
Underweight	38 (18.2%)	4 (3.2%)	<0.001	2 (3.0%)
Normal	130 (62.2%)	74 (58.7%)		41 (62.1%)
Overweight/Obese	41 (19.6%)	48 (38.1%)		23 (34.9%)
Education level, n(%)				
ISCED 4	49 (38.0%)	40 (18.5%)	<0.001	31 (31.3%)
ISCED 5	30 (23.3%)	81 (37.5%)		13 (13.1%)
ISCED 6	50 (38.7%)	95 (44.0%)		55 (55.6%)
Location, n(%)				
Aktobe	31 (23.7%)	26 (12.0%)	0.02	10 (10.1%)
Almaty	38 (29.0%)	59 (27.3%)		2 (2.0%)
Nur-Sultan	54 (41.2%)	112 (51.9%)		17 (17.2%)
Shymkent	8 (6.1%)	19 (8.8%)		70 (70.7%)
Type of payment, n(%)				
State-funded	51 (25.9%)	45 (36.6%)	0.04	16 (55.2%)
Self-paid	146 (74.1%)	78 (63.4%)		13 (44.8%)

Supplementary Table 5. Past and current medical history of infertility of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Comorbidity, n(%)				
Yes	76 (35.2%)	80 (61.1%)	<0.001	18 (18.2%)
No	140 (64.8%)	51 (38.9%)		81 (81.8%)
Infertility duration (years)				
Mean±SD	5.4±3.7	6.1±4.0	0.13	6.7±3.9
Median (IQR)	4.8 (3-7)	5 (3-8)		6.5 (4-9)
Number of previous deliveries, n(%)				
None	144 (66.7%)	90 (69.2%)	0.29	64 (65.3%)
One	50 (23.1%)	33 (25.4%)		29 (29.6%)
Two or more	22 (10.2%)	7 (5.4%)		5 (5.1%)
Number of previous miscarriages, n(%)				
None	190 (88.0%)	111 (85.4%)	0.49	83 (84.7%)
One or more	26 (12.0%)	19 (14.6%)		15 (15.3%)
Number of previous intentional pregnancy interruptions, n(%)				
None	198 (91.7%)	116 (89.2%)	0.45	90 (91.8%)
One or more	18 (8.3%)	14 (10.8%)		8 (8.2%)
Number of previous IVF cycles, n(%)				
None	179 (83.4%)	90 (68.7%)	<0.01	66 (68.7%)
One	18 (8.4%)	26 (19.8%)		23 (24.0%)
2 or more	18 (8.4%)	15 (11.5%)		7 (7.3%)
Cause of infertility, n(%)				
Female	97 (45.1%)	55 (42.3%)	0.32	66 (68.0%)
Male	16 (7.4%)	16 (12.3%)		9 (9.3%)
Mixed	102 (47.4%)	59 (45.4%)		22 (22.7%)

Supplementary Table 6. IVF treatment characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Number of oocytes retrieved				
Mean±SD	11.2±7.8	8.5±7.9	<0.01	11.6±9.4
Median (IQR)	10 (6-14)	7 (2-13)		6 (4-17)
Number of embryos transferred				
Mean±SD	1.7±0.8	1.7±1.9	0.10	4.7±4.9
Median (IQR)	2 (1-2)	1 (1-2)		2 (1-6.5)
Used protocol, n(%)				
Classic-long	23 (10.7%)	11 (8.4%)	0.27	2 (2.2%)
Classic-short	177 (82.3%)	114 (87.0%)		88 (97.8%)
Non-classic – natural cycle	4 (1.9%)	3 (2.3%)		0 (0%)
Non-classic – ultrashort	11 (5.1%)	2 (1.5%)		0 (0%)
Non-classic – stimulated in luteal phase	0 (0%)	1 (0.8%)		0 (0%)

Supplementary Table 7. Simple and multiple Poisson regression analyses of clinical setting and payment type predicting IVF clinical pregnancy (sensitivity analysis, excluding women from Astana private clinic (n=108) with the highest pregnancy rate).

Scales	**Clinical pregnancy**	
	Crude RR (95% CI)	**[&]Adjusted RR (95% CI)**
		Model A
Public clinics	0.47 (0.32; 0.70)*	0.54 (0.39; 0.75)*
		Model B
Public clinics	0.47 (0.32; 0.70)*	0.43 (0.27; 0.69)*
Publicly funded	0.80 (0.51; 1.25)	1.44 (0.90; 2.32)
	Model C	
	[&]Adjusted RR (95% CI)	
	Publicly funded	Self-paid
Public clinics	0.87 (0.32; 2.34)	0.34 (0.19; 0.63)

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl. Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

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Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

Running title: **Utilization of governmental support of IVF procedures**

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Abstract

Objectives

Infertility rates have been increasing in low- and middle-income countries, including Kazakhstan. The need for accessible and affordable assisted reproductive technologies has become essential for many subfertile women. We aimed to explore whether the public funding and clinical settings are associated with IVF clinical pregnancy and to determine whether the relationship between IVF clinical pregnancy and clinical settings is modified by payment type.

Design

A prospective cohort study

Setting

Three private and two public IVF clinics located in major cities

Participants

Women aged ≥ 18 seeking first or repeated IVF treatment and agreed to complete a survey were included in the study. Demographical and past medical history data were collected from a survey, while clinical data from medical records. The total response rate was 14%.

Primary and secondary outcome measures

Clinical pregnancy was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The outcome data were missing for 22% of women.

Results

Out of 446 women in the study, 68.2% attended private clinics. Two-thirds of women attending public clinics and 13% of women attending private clinics were publicly funded. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), and transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$), and had a statistically significantly higher pregnancy rate compared to public clinics (79.0% vs 29.7%, $p<0.001$). Publicly-funded women had on average a higher number of oocytes retrieved and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95%CI 1.02; 1.47) than self-paid women, after adjusting for covariates. There was no statistically significant interaction between clinical setting and payment type.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. There is also a need to further investigate whether the increase in public funding will influence clinical pregnancy rates.

Key words: Governmental support, financial support, utilization, Infertility; IVF treatment; Stress; Depression; Anxiety; Kazakhstan

Strengths and limitations of this study

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings in Kazakhstan.

Non-response bias may result in overestimation of the association between clinical settings and funding models with the IVF outcome because it is possible that non-respondents had a more likely poor prognosis.

22% of the study participants had unknown IVF outcomes and were excluded from the multivariable analysis.

Although we controlled for several covariates in the models, inclusion of additional variables such as behavioral, environmental factors, parental demographical characteristics, embryo quality, and experience and qualification of physicians could benefit future research in obtaining less biased results.

Introduction

Infertility is defined as an inability to conceive within 12 months of an unprotected sexual intercourse in women younger than 35 years or within 6 months in women older than 35 years.[1 2] Infertility affects a significant proportion of the population around the globe, and it is estimated to affect between 8 and 12% of reproductive-aged couples worldwide. [3-5] However, in some developing countries, the rates of infertility are much higher, reaching 25-30% in some populations.[3] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[6] Taking into consideration that the desire for parenthood is one of the basic human needs and rights, the worldwide problem with infertility becomes even more dramatic. In most societies, despite cultural or religious preferences, becoming a parent is perceived as an essential component in achieving self-realization and meaning in life.[7]

One of the most important issues in contemporary assisted reproductive technologies (ART) markets is access to the treatment.[8 9] As infertility is a medical condition, and couples with unfavorable fertility characteristics should have equal access to receive medical care, currently in many countries healthcare policymakers are trying to increase access to ART treatment for patients who cannot afford to pay out of pocket for the treatment.[8] Moreover, the relative cost that patients pay for ART treatment predicts not only the level of access but also the number of embryos transferred.[9] This fact makes insurance or governmental support is very important. There is a huge demand and unmet need for ART, especially in developing countries with a high rate of infertility.[6] A health economic report in 2002 put the lowest estimate of the global need for ART at 1,500 cycles per million populations per year, assuming that only 50% of couples who need ART will have it done.[10] At the same time, there is a large difference in both infertility services availability and quality between high- and low-income countries and between the rich and the poor in the same country,[11] particularly in ART procedures, which violates the basic ethical principles of justice, equity and equality.[8 11 12] However, some studies showed that insurance support to ART access can lead to a substantial increase in IVF usage in a market, [8] therefore, controlling by specific patient selection is required. This will ensure that the treatment for couples with severe medical needs will be available.

Despite an increasing medical demand for infertility treatments, public funding challenges for IVF exist in many developing countries.[13] While high-income countries like France, Spain, and Israel, provide full coverage of IVF treatments as a part of social policy, low-income countries cannot afford it. In the situation when coverage for IVF is absent or incomplete, it makes the IVF treatments unaffordable for couples with the most need. From both the public health and economic standpoint, the financial support of IVF may represent a good investment in terms of governmental financial returns, even in lower-income countries with state-financed health care systems such as Ukraine, Belarus, and Kazakhstan.[13] There is an interest to support IVF treatments from a governmental perspective. After successful IVF treatment, couples with fertility issues create new citizens who will eventually become future taxpayers. However, access to IVF is dependent not only on the particular country income but also on the efficiency of wealth distribution, and the health policy, and health insurance system.[8 13]

Kazakhstan is a developing Central Asian republic, and one of the countries with the highest regional prevalence of infertility.[3 13-16] Fertility as a cornerstone of family planning in Central Asian culture plays an important role in the strength of couples' relationships.[16] However, the fertility rate in Kazakhstan decreased significantly from 4.6 in 1960 to 2.8 in 2015,[15] and the prevalence of infertility varies from 12% to 15.5%.[14-16] Considering the infertility issue in Kazakhstan, the need for accessible and affordable assisted reproductive technologies (ART) is found to be very high.

A pioneer clinic for in vitro fertilization (IVF) in Kazakhstan was established in 1995 with the first newborn delivered in 1996. The first ART clinic was private, and before 2010 all expenses for IVF treatment had been paid by patients. Since 2010 the Ministry of Healthcare provides funds for IVF coverage and few public IVF clinics have been established. Apart from public IVF clinics, the public-funded IVF cycles are performed in private clinics as well. Although the funds are limited in amount, from 2010 through 2018 with the governmental support (quotas), around 3,000 babies were born with IVF procedure facilitation. According to the Kazakhstani State Program, in 2021 the government will fund 7,000 IVF cycles per year.[17] It is 7-times more than in 2020 (1,000 cycles). Considering the mentioned circumstances, it is very important to investigate factors that might have an impact on the IVF outcome and to understand how effectively governmental money has been utilized.

We aimed in this study to investigate whether public funding and clinical settings are associated with IVF clinical pregnancy and to determine whether the relationship between IVF clinical pregnancy and clinical settings is modified by payment type.

Methods

Study design

This prospective cohort study was conducted among women attending ART clinics between June 2019 and September 2020 in Kazakhstan. Women seeking first or repeated IVF treatment were asked to participate in the study, providing them with oral and written informed consent. The response rate was 14% (446 out of 3223). Adult women who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Women who were under 18 years old, who were not able to answer the survey questions in Kazakh, Russian or English languages and who refused to provide written informed consent were excluded. The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee (#120/28012019).

The study participants were enrolled from three private and two public ART clinics. All private clinics located in major cities are branches of one for-profit medical organization. This private organization was established in 1995 and performed the first IVF treatment in Kazakhstan. The public clinics were also from major cities – the National Research Center of Mother and Child Health (NRCMCH) in Nur-Sultan city and the Regional Perinatal Center in Aktobe city. The hospital-based public clinics have started providing ART treatment starting from 2007 and 2018, respectively. NRCMCH was accredited and certified according to the Joint Commission

International standards. Both private and public clinics are entitled to provide services paid out-of-pocket and under public funding.

IVF treatment is funded through public funding or self-payment (out-of-pocket). Subfertile patients could receive public funding for one IVF cycle per year within the State Guaranteed Health Benefits package of the Republic of Kazakhstan. To receive public funding, women must satisfy several inclusion criteria such as being Kazakhstani residents, being in the age range of 18-42 years old, having a good ovarian reserve, no severe comorbidities that could substantially reduce the probability of conceiving a child via IVF and no children. Women with ovarian or cervical benign or malignant tumors, acute inflammatory diseases, somatic or psychological diseases, and low ovarian reserve do not fall under the government support. Only 15 clinics, five public and ten private, are accredited to provide IVF services under the public funding scheme. On the other hand, self-paid women are not restricted in age, number of IVF cycles per year, or clinical setting where to undergo IVF treatment. For self-paid women, costs associated with IVF treatment range between US$1,200 – US$3,600 per one IVF cycle.

Study variables

The binary outcome variable was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The clinical pregnancy rate was calculated per egg retrieval cycle (cumulatively from fertilized fresh and frozen eggs). Patients were followed up for three months after an embryo(s) transfer. Patients with "unknown" status were those who have not yet reached 8 weeks gestation and have not yet had an ultrasound to determine the presence or absence of clinical pregnancy. Patients provided socio-demographic data such as age in years, body mass index (BMI), education level and payment type (publicly funded or self-paid) through a survey. BMI was categorized as underweight (less than 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and overweight/obese (25 kg/m^2 and above). According to the International Standard Classification of Education (ISCED), education level was grouped to ISCED 4 level—secondary high school, ISCED 5 level—post-secondary non-tertiary education and ISCED 6 level —bachelor or master level education. Patient past medical history data such as comorbidities associated with infertility, duration of infertility, number of previous deliveries, number of previous miscarriages, number of intentional pregnancy interruptions and number of previous IVF cycles were collected using a standardized survey. Clinical data about the number of oocytes retrieved, number of embryos transferred, cause of infertility (female, male and mixed), type of treatment protocol, and multiple pregnancies were collected from patients' medical records.

Statistical analysis

In the descriptive analysis, continuous variables were summarized as means or medians and corresponding variability measurements (standard deviations and inter-quartile ranges). Categorical variables were described in absolute and relative frequencies. To compare means between two-groups, independent t-test or Mann-Whitney U-test was used, where appropriate. To test independence between two categorical variables, the chi-square test or Fisher's exact test was performed. Simple and multiple Poisson regression modeling with robust estimation were

implemented to assess relationships of independent variables with the outcome variable. Since the number of oocytes retrieved is considered a strong predictor for the clinical pregnancy, [18 19] we additionally constructed linear regression models to test associations of independent variables with the number of oocytes retrieved. Models were built according to the parsimonious principle, including a reasonable number of covariates based on their clinical, epidemiological importance and statistical significance. We hypothesized that the payment type and clinical setting would be highly associated, and inclusion both would result in multicollinearity. However, no multicollinearity was observed. To check multicollinearity, we utilized the variance inflation factor and examined changes in coefficients and its standard errors by adding and removing these variables from the models. We decided to include both variables in the regression modeling as private clinics look for additional income by treating publicly funded patients, likewise, public clinics are encouraged to provide out-of-pocket services. No interaction was observed between payment type and clinical setting at significance level of 0.05. Nonetheless, we presented results from the model with the interaction between clinical settings and payment type, as it was practically important to see whether the outcomes differ between private and public clinics depending on payment type. We also checked for other interactions. An interaction between comorbidity and the clinical settings was found statistically significant. Lastly, we examined the goodness-of-fit of the final models using Pearson's and deviance goodness-of-fit tests. The goodness-of-fit statistics were non-significant, indicating that the models fitted well enough to the sample data.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Four hundred forty-six women attending IVF clinics agreed to participate in the study. The average age of the participants was 33.8±5.6 years (Table 1). One-third of women were overweight or obese (27.9%), approximately half of them had education level at ISCED 6 (45.1%), and two-thirds paid themselves (out-of-pocket) for IVF treatment (67.9%). On average, infertility duration was 5.9±3.9 years (Table 2). A female factor as a cause of infertility was determined in half of the women, while in others factor was mixed or male, and a quarter of the women had previously attempted at least one IVF cycle treatment (24.2%). Most women were treated with short or long classic protocol, and the cumulative pregnancy rate reached 62.2% (Table 3).

Table 1. Socio-demographic characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Age (years), mean±SD	33.8±5.6	33.9±4.9	33.7±5.9	0.81
Missing data=2%				
BMI, n(%)				
Underweight	44 (11.0)	10 (7.3%)	34 (12.9%)	<0.01
Normal	245 (61.1)	76 (55.5%)	169 (64.0%)	
Overweight/Obese	112 (27.9)	51 (37.2%)	61 (23.1%)	
Missing data=10%				
Education level, n(%)				
ISCED 4	120 (27.0%)	51 (36.4%)	69 (22.7%)	<0.01
ISCED 5	124 (27.9%)	26 (18.6%)	98 (32.2%)	

ISCED 6	200 (45.1%)	63 (45.0%)	137 (45.1%)	
Missing data=0.5%				
Location, n(%)				
Aktobe	67 (15.0%)	67 (47.2%)	0 (0%)	
Almaty	99 (22.2%)	0 (0%)	99 (32.6%)	
Nur-Sultan	183 (41.0%)	75 (52.8%)	108 (35.5%)	
Shymkent	97 (21.8%)	0 (0%)	97 (31.9%)	
Missing data=0%				
Payment type, n(%)				
Publicly funded	112 (32.1%)	85 (59.9%)	27 (13.0%)	<0.001
Self-paid	237 (67.9%)	57 (40.1%)	180 (87.0%)	
Missing data=21.8%				

Table 2. Past IVF medical history of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Comorbidity, n(%)				
Yes	174 (39.0%)	83 (58.4%)	91 (29.9%)	<0.001
No	272 (61.0%)	59 (41.6%)	213 (70.1%)	
Missing data=0%				
Infertility duration (years)				
Mean±SD	5.9±3.9	6.0±3.5	5.9±4.1	0.75
Median (IQR)	5 (3-8)	6 (3-8)	5 (3-8)	
Missing data=5.6%				
Number of previous deliveries, n(%)				
None	298 (67.1%)	106 (74.6%)	192 (63.6%)	<0.001
One	112 (25.2%)	36 (25.4%)	76 (25.2%)	
2 or more	34 (7.7%)	0 (0%)	34 (11.2%)	
Missing data=0.5%				
Number of previous miscarriages, n(%)				
None	384 (86.5%)	127 (89.4%)	257 (85.1%)	0.21
One or more	60 (13.5%)	15 (10.6%)	45 (14.9%)	
Missing data=0.5%				
Number of previous intentional pregnancy interruptions, n(%)				
None	404 (91.0%)	125 (88.0%)	279 (92.4%)	0.14
One or more	40 (9.0%)	17 (12.0%)	23 (7.6%)	
Missing data=0.5%				
Number of previous IVF cycles, n(%)				
None	335 (75.8%)	106 (75.2%)	229 (76.1%)	0.41
One	67 (15.2%)	25 (17.7%)	42 (13.9%)	
2 or more	40 (9.0%)	10 (7.1%)	30 (10.0%)	
Missing data=0.9%				
Cause of infertility, n(%)				
Female	218 (49.3%)	57 (40.4%)	161 (53.5%)	<0.01
Male	41 (9.3%)	8 (5.7%)	33 (11.0%)	
Mixed	183 (41.4%)	76 (53.9%)	107 (35.5%)	
Missing data=0.9%				

Table 3. Clinical IVF characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Number of oocytes retrieved				
Mean±SD	10.5±2.0	8.1±7.2	11.5±8.4	<0.001
Median (IQR)	1 (0-2)			
Missing data=9%				
Number of embryos transferred				
Mean±SD	2.0±2.2	1.4±1.1	2.2±2.5	<0.001
Median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	
Missing data=14.8%				
Used protocol				
Classic-long	36 (8.3%)	5 (3.7%)	31 (10.3%)	0.06
Classic-short	379 (86.9%)	122 (90.4%)	257 (85.4%)	

Non-classic – natural cycle	7 (1.6%)	2 (1.5%)	5 (1.7%)	
Non-classic – ultrashort	13 (3.0%)	5 (3.75)	8 (2.7%)	
Non-classic – stimulated in luteal phase	1 (0.2%)	1 (0.7%)	0 (0%)	
Missing data=2.2%				
Clinical pregnancy, n (%)				
Yes	216 (62.2%)	35 (29.7%)	181 (79.0%)	<0.001
No	131 (37.8%)	83 (70.3%)	48 (21.0%)	
Missing data=22.2%				
Clinical pregnancy rate per embryos transferred, %	38.3	22.0	44.7	<0.01
Missing data=22.2%				
Multiple pregnancies, n(%)				
Yes	4 (1.0%)	0 (0%)	4 (1.4%)	0.32
No	418 (99.0%)	131 (100%)	287 (98.6%)	
Missing data=5%				

Public vs private clinics.

More than two-thirds of women attended private clinics (68.2%). There were no differences in age (p=0.81), infertility duration (p=0.75), number of previous miscarriages (p=0.21), number of previous intentional pregnancy interruptions (0.14), and number of previous IVF cycles (p=0.41) between participants of public and private clinics (Table 2). Public clinics had statistically significantly higher proportions of overweight or obese women (p<0.01), patients with education level at ISCED 4 (p<0.01) and patients who were publicly funded (p<0.001) than private clinics. The proportion of patients with comorbidities was also higher in public clinics (58.4% vs 29.9%, p<0.001) than in private clinics. However, the percentage of women with a history of previous deliveries (p<0.001) and the proportion of patients who had a female factor as a cause of infertility (p<0.01) were statistically significantly higher among patients in private clinics. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had more multiple pregnancies (0 vs 4, p=0.32) than public clinics (Table 3). Private clinics had a statistically significantly higher cumulative pregnancy rate (79.0% vs 29.7%, p<0.001) and higher clinical pregnancy rate per embryos transferred (44.7% vs 22.0%, p<0.01) compared to public clinics.

Publicly funded vs self-paid

One-third of women (32.1%) received public funding for IVF treatment. There was no difference between publicly funded and self-paid patients in terms of age, BMI, comorbidity, number of previous miscarriages and number of previous intentional pregnancy interruptions (Supplementary Tables 1-2). Despite that the number of oocytes retrieved, the number of embryos transferred, and type of treatment protocol used were comparable in the two groups, cumulative clinical pregnancy rates were statistically significantly different between them (53.1% vs 65.2%, p=0.04, publicly funded vs self-paid, respectively, Supplementary Table 3).

Factors associated with IVF outcomes.

In bivariable analysis, clinical pregnancy was statistically significantly associated with BMI, education level, location, type of payment, history of comorbidity, number of previous IVF cycles and number of oocytes retrieved during IVF treatment (Supplementary Tables 4-6).

Table 4. Simple and multiple Linear and Poisson regression analyses of clinical settings and payment type predicting the number of oocytes retrieved and IVF clinical pregnancy.

	Number of oocytes retrieved		**Clinical pregnancy**	
	Crude β-coefficient (95% CI)	**†Adjusted β-coefficient (95% CI)**	**Crude RR (95% CI)**	**&Adjusted RR (95% CI)**
	Model 1		Model 3	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-3.7 (-5.5; 1.9)	0.38 (0.26; 0.54)*	0.44 (0.33; 0.59)*
	Model 2		Model 4	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-5.6 (-7.8; -3.4)*	0.38 (0.26; 0.54)*	0.39 (0.29; 0.52)*
Self-paid	Reference	Reference	Reference	Reference
Publicly funded	-0.2 (-2.0; 1.7)	3.3 (1.1; 5.5)*	0.82 (0.59; 1.12)	1.23 (1.02; 1.47)*

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles
& Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.
*p<0.05
RR = relative risk, CI = confidence interval.

Table 5. The relationship of clinical settings modified by the funding model with the number of oocytes retrieved and IVF clinical pregnancy using multiple Linear and Poisson regression analyses.

	†Adjusted β-coefficient (95% CI) for number of oocytes retrieved		**p-value**	**&Adjusted RR (95% CI) for clinical pregnancy**		**p-value**
	Publicly funded	Self-paid		Publicly funded	Self-paid	
Private clinics	Reference	Reference	0.10	Reference	Reference	0.19
Public clinics	-3.31 (-6.81; 0.19)	-6.86 (-9.49; -4.22)		0.46 (0.33; 0.64)	0.30 (0.17; 0.54)	

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles
& The model was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.
*p<0.05
RR = relative risk, CI = confidence interval, p-values are calculated for interaction terms.

Public clinics on average retrieved a lower number of oocytes than private clinics (estimated β-coefficient= -5.6, 95% CI -7.8; -3.4) controlling for payment type and other covariates (Table 4). While adjusting for the number of oocytes retrieved, the number of embryos transferred and payment type, IVF procedures in public clinics were independently negatively associated with the clinical pregnancy (RR=0.39, 95% CI 0.29; 0.52). Women who were publicly funded for IVF treatment had on average a higher number of oocytes retrieved (estimated β-coefficient=3.3, 95% CI 1.1; 5.5) and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95% CI 1.02; 1.47) than those who were self-paid in the multiple regression models.

Even though the relationship between clinical settings and the IVF clinical pregnancy rate was not modified by the payment type (p=0.19), we noticed that women who paid out of pocket had a

stronger negative association with the IVF clinical pregnancy rate (and had a relatively lower number of oocytes retrieved) than patients who were publicly funded, among women who attended public clinics (Table 5). There was, additionally, a statistically significant interaction between clinical settings and comorbidity in predicting IVF clinical pregnancy. The adjusted relative risk of clinical pregnancy between public clinics vs private clinics among patients with no history of comorbidities was 0.72 (0.54; 0.95), while among those with a history of at least one comorbidity was 0.13 (0.07; 0.26) adjusted for covariates.

Discussion

This is the first multicenter study conducted comparing IVF outcomes between private and public clinics in Kazakhstan. The study results show that the private clinics had a substantially higher clinical pregnancy rate. This difference could be partially explained by the more rigorous selection of subfertile women with better IVF prognosis in private clinics. Indeed, our study results confirm it: the private clinics had a lower percentage of overweight or obese women and a lower proportion of women with comorbidities than public clinics. Previous studies have shown that higher BMI levels and infertility-related comorbidities were negatively predictive of IVF outcomes.[18 20] In addition, the private clinics retrieved and transferred a statistically significantly higher number of oocytes and embryos, respectively. A systematic review and meta-analysis by Van Loendersloot et al illustrated that a higher number of oocytes retrieved, and a higher number of embryos transferred were positively associated with successful IVF outcomes.[18] As treatment costs per an IVF cycle are high, patients in private clinics want to maximize the likelihood to conceive a child by retrieving and transferring more oocytes and embryos in a given IVF cycle.[21] However, transferring more embryos is associated with multiple pregnancies.[22] Indeed, our study results found that all multiple pregnancies occurred among women attending private clinics. Multiple pregnancies are not only associated with higher risks of morbidity and mortality for mothers during pregnancy,[23] but also with greater total pregnancy costs, antenatal care and delivery costs when compared with singleton births.[24] Introduction of insurance coverage or public funding of reproductive treatment in many countries has resulted in the reduction of the number of embryos transferred per cycle, consequently, decreased incidence rates of multiple pregnancies[21 25 26] and reduced associated healthcare and patient costs.

After controlling for covariates, patients in public clinics still were less likely to conceive a child than patients in private clinics. Independent from the number of oocytes retrieved and number of embryos transferred, public clinics had lower clinical pregnancy rates. To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 7). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[16] The sensitivity analysis revealed that the public clinics were still independently associated with lower clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates.

Given that we controlled for important confounding variables in the models, lower pregnancy rates in public clinics could be attributed to other factors. First, while patients with better prognoses remain on long waiting lists in public clinics, they undergo their first IVF cycles in private clinics. Thus, patients with a higher likelihood of conceiving a child are treated in private clinics whereas public clinics treat patients with worse prognosis and longer infertility duration as they remain on the long waiting lists.[27] Second, patients with higher socioeconomic status are likely to choose private clinics. Previous studies have shown that patients from poor socioeconomic communities had lower levels of anti-Mullerian hormone and antral follicle count, indicating reduced ovarian reserve and a lower probability of conceiving a child.[28] Third, private clinics are likely to recruit and retain, with better salary offers and benefits, more skillful and experienced physicians who are able to retrieve sufficient quantity and quality of oocytes and to perform a higher number of successful embryo transfer procedures. Several studies have suggested that a "physician factor" is an important predictor of successful IVF outcomes[29] align with the number of oocytes retrieved,[30] number of high-quality embryos transferred and absence of blood or mucus on the transfer catheter.[31] In fact, in the bivariable analysis, the clinical pregnancy rate per embryos transferred was higher in private clinics, suggesting higher-quality embryos transferred leading to successful outcomes. The results of the linear regression models showed that public clinics, on average, retrieved a low number of oocytes. This finding support two explanations listed above. Low oocytes retrieval in public clinics could indicate higher proportions of patients with poor prognosis (reduced ovarian reserve) or less skillfulness and experience of physicians working in public clinics who are not able to retrieve an adequate quantity and quality eggs. Lastly, private clinics potentially continuously update their equipment to provide advanced and high-technology care. Latest technologies foster patient-centered care by allowing more data collection that can be used for personalized and more effective IVF treatment.

Based on previous studies, we expected that publicly funded women would have a lower pregnancy rate than women who self-paid because public funding eliminates barriers related to treatment costs and encourages women with worse prognoses to seek IVF treatment.[21 25 26] However, public funding is not widely available in Kazakhstan and only a small percentage of subfertile women receive funding. Thus, those who are selected to receive state funding usually have a higher probability of conceiving a child.[32] Indeed, our study results showed that publicly funded women had a higher likelihood of conceiving a child than self-paid women. Bureaucratic barriers, in addition, discourage financially disadvantaged patients from applying for public funding and seeking IVF treatment. While financially independent patients who do not meet public funding criteria – because of their worse reproductive prognosis – seek IVF treatment by paying out-of-pocket. This speculation is supported by the findings from the multiple linear regression modeling factors associated with the number of oocytes retrieved. In the linear model, independent from other factors, patients who were publicly funded had a higher number of oocytes retrieved than self-paid women which indicates that self-paid patients had reduced ovarian reserve, thus, the lower probability to become pregnant.[19] It is likely that when public funding becomes more widely available in Kazakhstan, the utilization of IVF services will increase and not only women with better reproductive prognoses will access IVF treatment, but also patients with poor prognosis. Thus, the relative number of women with poor reproductive prognoses is expected to proportionally increase.[33] Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.[34]

Since government-funded IVF cycles can be performed in both clinical settings as the government encourages the private sector to provide health care services under the governmental support and similarly, the public sector is stimulated to provide services on a self-paid basis, it was of the study interest to investigate the interaction between clinical settings and funding type in predicting the IVF outcome. Despite that the interaction between clinical setting and payment type was not statistically significant, we found that among self-paid women attending public clinics had a stronger negative association with IVF outcomes (relatively lower number of oocytes retrieved and lower clinical pregnancy rates) than among women who were publicly funded. There is a need to conduct further studies to investigate the existence of the interaction between the clinical settings and payment type among IVF patients. Also, we found that patients with a history of at least one comorbidity and attending public clinics had the lowest probability of conceiving a child. Patients with more severe comorbidities likely undergo IVF cycles in public clinics because they might have been refused to be treated in private clinics – the more rigorous selection process of subfertile women with better IVF prognosis is in place. Previous studies have shown that medical comorbidities were negatively associated with IVF pregnancy rates.[35 36] However, none of the studies examined the effect modification of medical comorbidities on the relationship between clinical setting and IVF outcomes.

Strengths and limitations

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings in Kazakhstan. The multivariable analysis that included clinically and epidemiologically important variables in the models allowed us to examine independent relationships of the clinical settings and payment type with the IVF outcomes. In addition, sensitivity analysis provided more robust results in concluding.

Several study limitations that should be mentioned. Firstly, non-response bias could be present as the response rate was very low (14%). Since descriptive data on non-respondents were not collected for comparison, we were not able to confirm or exclude non-response bias. Overall, given the low response rate, the generalizability of the study results should be considered with caution. Secondly, data on IVF outcomes were unknown for 22% of the study participants. The associations of the IVF outcomes with poor prognosis predictors could be underestimated, as women with unknown IVF outcomes had poor prognosis (were likely overweight or obese, had the longest infertility duration and a higher proportion of those who previously attempted IVF cycles) and were not included in the multivariable analysis.[37] Thirdly, other important variables that could potentially affect IVF outcomes were not collected. Although we controlled for several covariates in the models, inclusion of additional variables (behavioral factors – smoking, alcohol consumption, physical activity; environmental factors; parental demographical characteristics; embryo quality; experience and qualification of physicians; and number of times embryos transfers were performed within one egg retrieval cycle) could benefit future research in obtaining less biased results. Lastly, the small sample size in the regression models did not allow to obtain more robust estimates of the effect sizes of the independent variables and examine other potential interactions among them.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. The difference in IVF pregnancy rates between private and public clinics is not only associated with demographical and clinical characteristics of patients but also could be related to factors associated with the clinical settings. There is also a need to further investigate whether the increase in public funding would influence clinical pregnancy rates and potentially live birth rates among subfertile women.

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Contributors

GB and MT conceived the study. AI and MT contributed to the study design. GA, ST, TU, SB, AA, GU, ZD, GBe, and AB contributed to the acquisition of data. AI, MT, and GA contributed to data analysis and have verified the underlying data. AI, GA, and ST contributed to the initial drafting of the manuscript. GA, GB, TU, SB, AB, and MT contributed to study supervision. AI, GA, and MT contributed to reviewing and finalizing the manuscript. All authors approved the final version of the report and agree to be accountable for all aspects of the work.

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Competing interests

SB is a paid employee of Ecomed IVF private clinic.

Patient consent for publication

Not required.

Ethics statement

The University Medical Center Institutional Research Ethics Committee(№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee(#120/28012019)

Data availability statement

Data can be requested from the corresponding author.

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Supplementary Tables

Supplementary Table 1. Socio-demographic characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Age (years), mean±SD	34.2±4.8	34.2±5.9	0.99	32.1±5.7
BMI, n(%)				
Underweight	12 (10.8%)	32 (13.9%)	0.62	0 (0%)
Normal	69 (62.2%)	132 (57.1%)		44 (74.6%)
Overweight/Obese	30 (27.0%)	67 (29.0%)		15 (25.4%)
Education level, n(%)				
ISCED 4	39 (34.8%)	47 (20.0%)	<0.01	34 (35.1%)
ISCED 5	27 (24.1%)	90 (38.3%)		7 (7.2%)
ISCED 6	46 (41.1%)	98 (41.7%)		57.7%)
Location, n(%)				
Aktobe	41 (36.6%)	26 (11.0%)	<0.001	0 (0%)
Almaty	3 (2.7%)	96 (40.5%)		0 (0%)
Nur-Sultan	68 (60.7%)	115 (48.5%)		0 (0%)
Shymkent	0 (0%)	0 (0%)		97 (100%)

Supplementary Table 2. Past and current medical history of infertility of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Comorbidity, n(%)				
Yes	49 (43.7%)	125 (52.7%)	0.12	0 (0%)
No	63 (56.3%)	112 (47.3%)		97 (100%)
Infertility duration (years)				
Mean±SD	6.6±3.6	5.1±3.9	<0.01	7.0±3.9
Median (IQR)	6 (4-8)	4 (3-7)		6 (4-9.5)
Number of previous deliveries, n(%)				
None	87 (77.7%)	150 (63.5%)	<0.01	61 (63.5%)
One	24 (21.4%)	62 (26.3%)		26 (27.1%)
Two or more	1 (0.9%)	24 (10.2%)		9 (9.4%)
Number of previous miscarriages, n(%)				
None	100 (89.3%)	205 (86.9%)	0.52	79 (82.3%)
One or more	12 (10.7%)	31 (13.1%)		17 (17.7%)
Number of previous intentional pregnancy interruptions, n(%)				
None	101 (90.2%)	209 (88.6%)	0.65	94 (97.9%)
One or more	11 (9.8%)	27 (11.4%)		2 (2.1%)
Number of previous IVF cycles, n(%)				
None	84 (75.7%)	184 (78.6%)	0.03	67 (69.1%)
One	20 (18.0%)	22 (9.4%)		25 (25.8%)
2 or more	7 (6.3%)	28 (12.0%)		5 (5.1%)
Cause of infertility, n(%)				
Female	35 (31.2%)	106 (45.3%)	<0.01	77 (80.2%)
Male	6 (5.4%)	22 (9.4%)		13 (13.5%)
Mixed	71 (63.4%)	106 (45.3%)		6 (6.3%)

Supplementary Table 3. IVF treatment characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Number of oocytes retrieved				
Mean±SD	10.2±8.0	10.3±8.1	0.87	11.2±8.8
Median (IQR)	9 (4-14)	9 (4-14)		9 (4-14)
Number of embryos transferred				
Mean±SD	1.6±1.0	1.5±0.8	0.93	4.5±4.8
Median (IQR)	2 (1-2)	2 (1-2)		2 (1-6)
Used protocol, n(%)				
Classic-long	7 (6.6%)	28 (12.0%)	0.09	1 (1.0%)
Classic-short	94 (89.5%)	189 (80.8%)		96 (99.0%)
Non-classic – natural cycle	2 (1.9%)	5 (2.1%)		0 (0%)
Non-classic – ultrashort	1 (1.0%)	12 (5.1%		0 (0%)
Non-classic – stimulated in luteal phase	1 (1.0%)	0 (0%)		0 (0%)
Clinical pregnancy, n (%)				
Yes	51 (53.1%)	146 (65.2%)	0.04	19 (70.4%)
No	45 (46.9%)	78 (34.8%)		8 (29.6%)
Miscarriage, n(%)				
Yes	0 (0%)	1 (0.4%)	1.00	0 (0%)
No	102 (100%)	225 (99.6%)		24 (100%)
Multiple pregnancies, n(%)				
Yes	1 (1.0%)	3 (1.3%)	1.00	0 (0%)
No	103 (99.0%)	226 (98.7%)		89 (100%)

Supplementary Table 4. Socio-demographic characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Age (years), mean±SD	33.7±5.9	34.5±5.2	0.21	33.0
BMI, n(%)				
Underweight	38 (18.2%)	4 (3.2%)	<0.001	2 (3.0%)
Normal	130 (62.2%)	74 (58.7%)		41 (62.1%)
Overweight/Obese	41 (19.6%)	48 (38.1%)		23 (34.9%)
Education level, n(%)				
ISCED 4	49 (38.0%)	40 (18.5%)	<0.001	31 (31.3%)
ISCED 5	30 (23.3%)	81 (37.5%)		13 (13.1%)
ISCED 6	50 (38.7%)	95 (44.0%)		55 (55.6%)
Location, n(%)				
Aktobe	31 (23.7%)	26 (12.0%)	0.02	10 (10.1%)
Almaty	38 (29.0%)	59 (27.3%)		2 (2.0%)
Nur-Sultan	54 (41.2%)	112 (51.9%)		17 (17.2%)
Shymkent	8 (6.1%)	19 (8.8%)		70 (70.7%)
Type of payment, n(%)				
State-funded	51 (25.9%)	45 (36.6%)	0.04	16 (55.2%)
Self-paid	146 (74.1%)	78 (63.4%)		13 (44.8%)

Supplementary Table 5. Past and current medical history of infertility of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Comorbidity, n(%)				
Yes	76 (35.2%)	80 (61.1%)	<0.001	18 (18.2%)
No	140 (64.8%)	51 (38.9%)		81 (81.8%)
Infertility duration (years)				
Mean±SD	5.4±3.7	6.1±4.0	0.13	6.7±3.9
Median (IQR)	4.8 (3-7)	5 (3-8)		6.5 (4-9)
Number of previous deliveries, n(%)				
None	144 (66.7%)	90 (69.2%)	0.29	64 (65.3%)
One	50 (23.1%)	33 (25.4%)		29 (29.6%)
Two or more	22 (10.2%)	7 (5.4%)		5 (5.1%)
Number of previous miscarriages, n(%)				
None	190 (88.0%)	111 (85.4%)	0.49	83 (84.7%)
One or more	26 (12.0%)	19 (14.6%)		15 (15.3%)
Number of previous intentional pregnancy interruptions, n(%)				
None	198 (91.7%)	116 (89.2%)	0.45	90 (91.8%)
One or more	18 (8.3%)	14 (10.8%)		8 (8.2%)
Number of previous IVF cycles, n(%)				
None	179 (83.4%)	90 (68.7%)	<0.01	66 (68.7%)
One	18 (8.4%)	26 (19.8%)		23 (24.0%)
2 or more	18 (8.4%)	15 (11.5%)		7 (7.3%)
Cause of infertility, n(%)				
Female	97 (45.1%)	55 (42.3%)	0.32	66 (68.0%)
Male	16 (7.4%)	16 (12.3%)		9 (9.3%)
Mixed	102 (47.4%)	59 (45.4%)		22 (22.7%)

Supplementary Table 6. IVF treatment characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Number of oocytes retrieved				
Mean±SD	11.2±7.8	8.5±7.9	<0.01	11.6±9.4
Median (IQR)	10 (6-14)	7 (2-13)		6 (4-17)
Number of embryos transferred				
Mean±SD	1.7±0.8	1.7±1.9	0.10	4.7±4.9
Median (IQR)	2 (1-2)	1 (1-2)		2 (1-6.5)
Used protocol, n(%)				
Classic-long	23 (10.7%)	11 (8.4%)	0.27	2 (2.2%)
Classic-short	177 (82.3%)	114 (87.0%)		88 (97.8%)
Non-classic – natural cycle	4 (1.9%)	3 (2.3%)		0 (0%)
Non-classic – ultrashort	11 (5.1%)	2 (1.5%)		0 (0%)
Non-classic – stimulated in luteal phase	0 (0%)	1 (0.8%)		0 (0%)

Supplementary Table 7. Simple and multiple Poisson regression analyses of clinical setting and payment type predicting IVF clinical pregnancy (sensitivity analysis, excluding women from Astana private clinic (n=108) with the highest pregnancy rate).

Scales	**Clinical pregnancy**	
	Crude RR (95% CI)	**[&]Adjusted RR (95% CI)**
		Model A
Public clinics	0.47 (0.32; 0.70)*	0.54 (0.39; 0.75)*
		Model B
Public clinics	0.47 (0.32; 0.70)*	0.43 (0.27; 0.69)*
Publicly funded	0.80 (0.51; 1.25)	1.44 (0.90; 2.32)
	Model C	
	[&]Adjusted RR (95% CI)	
	Publicly funded	Self-paid
Public clinics	0.87 (0.32; 2.34)	0.34 (0.19; 0.63)

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl. Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

Running title: **Utilization of governmental support of IVF procedures**

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Abstract

Objectives

Infertility rates have been increasing in low- and middle-income countries, including Kazakhstan. The need for accessible and affordable assisted reproductive technologies has become essential for many subfertile women. We aimed to explore whether the public funding and clinical settings are associated with IVF clinical pregnancy and to determine whether the relationship between IVF clinical pregnancy and clinical settings is modified by payment type.

Design

A prospective cohort study

Setting

Three private and two public IVF clinics located in major cities

Participants

Women aged ≥ 18 seeking first or repeated IVF treatment and agreed to complete a survey were included in the study. Demographical and past medical history data were collected from a survey, while clinical data from medical records. The total response rate was 14%.

Primary and secondary outcome measures

Clinical pregnancy was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The outcome data were missing for 22% of women.

Results

Out of 446 women in the study, 68.2% attended private clinics. Two-thirds of women attending public clinics and 13% of women attending private clinics were publicly funded. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), and transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$), and had a statistically significantly higher pregnancy rate compared to public clinics (79.0% vs 29.7%, $p<0.001$). Publicly-funded women had on average a higher number of oocytes retrieved and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95%CI 1.02; 1.47) than self-paid women, after adjusting for covariates. There was no statistically significant interaction between clinical setting and payment type.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. There is also a need to further investigate whether the increase in public funding will influence clinical pregnancy rates.

Key words: Governmental support, financial support, utilization, Infertility; IVF treatment; Stress; Depression; Anxiety; Kazakhstan

Strengths and limitations of this study

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings in Kazakhstan.

Non-response bias may result in overestimation of the association between clinical settings and funding models with the IVF outcome because it is possible that non-respondents had a more likely poor prognosis.

22% of the study participants had unknown IVF outcomes and were excluded from the multivariable analysis.

Although we controlled for several covariates in the models, inclusion of additional variables such as behavioral, environmental factors, parental demographical characteristics, embryo quality, and other factors could benefit future research in obtaining less biased results.

Introduction

Infertility is defined as an inability to conceive within 12 months of an unprotected sexual intercourse in women younger than 35 years or within 6 months in women older than 35 years.[1 2] Infertility affects a significant proportion of the population around the globe, and it is estimated to affect between 8% and 12% of reproductive-aged couples worldwide. [3-5] However, in some developing countries, the rates of infertility are much higher, reaching 25-30% in some populations.[3] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[6] Taking into consideration that the desire for parenthood is one of the basic human needs and rights, the worldwide infertility problem becomes even more dramatic. In most societies, despite cultural or religious preferences, becoming a parent is perceived as an essential component in achieving self-realization and meaning in life.[7]

One of the most important issues in contemporary assisted reproductive technologies (ART) markets is access to the treatment.[8 9] As infertility is a medical condition, and couples with unfavorable fertility characteristics should have equal access to receive medical care. Currently in many countries, healthcare policymakers are trying to increase access to ART treatment for patients who cannot afford to pay out of pocket for the treatment.[8] Moreover, the relative cost that patients pay for ART treatment predicts not only the level of access but also the number of embryos transferred.[9] This fact makes insurance or governmental support is very important. There is a huge demand and unmet need for ART, especially in developing countries with a high infertility rate.[6] A health economic report in 2002 put the lowest estimate of the global need for ART at 1,500 cycles per million populations per year, assuming that only 50% of couples who need ART will have it done.[10] At the same time, there is a large difference in both infertility services availability and quality between high- and low-income countries and between the rich and the poor within the same country,[11] particularly in ART procedures, which violates the basic ethical principles of justice, equity and equality.[8 11 12] However, some studies showed that insurance support to ART access can lead to a substantial increase in in vitro fertilization (IVF) usage in a market, [8] therefore, controlling by specific patient selection is required. This will ensure that the treatment for couples with severe medical needs will be available.

Despite an increasing medical demand for infertility treatments, public funding challenges for IVF exist in many developing countries.[13] While high-income countries like France, Spain, and Israel, provide full coverage of IVF treatments as a part of social policy, low-income countries cannot afford it. In the situation when coverage for IVF is absent or incomplete, it makes the IVF treatments unaffordable for couples with the most need. From both the public health and economic standpoint, the financial support of IVF may represent a good investment in terms of governmental financial returns, even in lower-income countries with state-financed health care systems such as Ukraine, Belarus, and Kazakhstan.[13] There is an interest to support IVF treatments from a governmental perspective. After successful IVF treatment, subfertile couples give births to new citizens who will eventually become future taxpayers. However, access to IVF is dependent not only on the particular country income but also on the efficiency of wealth distribution, and the health policy, and health insurance system.[8 13]

Kazakhstan is a developing Central Asian republic, and one of the countries with the highest regional infertility prevalence.[3 13-16] Fertility as a cornerstone of family planning in Central Asian culture plays an important role in the strength of couples' relationships.[16] However, the fertility rate in Kazakhstan decreased significantly from 4.6 in 1960 to 2.8 in 2015,[15] and the infertility prevalence varies from 12% to 15.5%.[14-16] Considering the infertility issue in Kazakhstan, the need for accessible and affordable ART is found to be very high.

A pioneer clinic for IVF in Kazakhstan was established in 1995 with the first newborn delivered in 1996. The first ART clinic was private, and before 2010 all expenses for IVF treatment had been paid by patients. Since 2010 the Ministry of Healthcare provides funds for IVF coverage, and few public IVF clinics have been established. Apart from public IVF clinics, the public-funded IVF cycles are performed in private clinics as well. Although the funds are limited in amount, from 2010 through 2018 with the governmental support (quotas), around 3,000 babies were born with IVF procedure facilitation. According to the Kazakhstan State Program, in 2021 the government has started funding 7,000 IVF cycles per year.[17] It is 7-times more than in 2020 (1,000 cycles). Considering the mentioned circumstances, it is very important to investigate factors that might have an impact on the IVF outcome and to understand how effectively governmental money has been utilized.

We aimed in this study to investigate the following research questions: "Are public funding and clinical settings associated with higher IVF clinical pregnancy rates?" and "Is the relationship between IVF clinical pregnancy and clinical settings modified by payment type?"

Methods

Study design

This prospective cohort study was conducted among women attending ART clinics between June 2019 and September 2020 in Kazakhstan. Women seeking first or repeated IVF treatment were asked to participate in the study, providing them with oral and written informed consent. The response rate was 14% (446 out of 3223). Adult women who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Women who were under 18 years old, who were not able to answer the survey questions in Kazakh, Russian or English languages and who refused to provide written informed consent were excluded. The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee (#120/28012019).

The study participants were enrolled from three private and two public ART clinics. All private clinics located in major cities are branches of one for-profit medical organization. This private organization was established in 1995 and performed the first IVF treatment in Kazakhstan. The public clinics were also from major cities – the National Research Center of Mother and Child Health (NRCMCH) in Nur-Sultan city and the Regional Perinatal Center in Aktobe city. The hospital-based public clinics have started providing ART treatment starting from 2007 and 2018, respectively. NRCMCH was accredited and certified according to the Joint Commission

International standards. Both private and public clinics are entitled to provide services paid out-of-pocket and under public funding.

IVF treatment is funded through public funding or self-payment (out-of-pocket). Subfertile patients could receive public funding for one IVF cycle per year within the State Guaranteed Health Benefits package of the Republic of Kazakhstan. To receive public funding, women must satisfy several inclusion criteria such as being Kazakhstani residents, being in the age range of 18-42 years old, having a good ovarian reserve, no severe comorbidities that could substantially reduce the probability of conceiving a child via IVF and no children. Women with ovarian or cervical benign or malignant tumors, acute inflammatory diseases, somatic or psychological diseases, and low ovarian reserve do not fall under the government support. Only 15 clinics, five public and ten private, are accredited to provide IVF services under the public funding scheme. On the other hand, self-paid women are not restricted in age, number of IVF cycles per year, or clinical setting where to undergo IVF treatment. For self-paid women, costs associated with IVF treatment range between US$1,200 – US$3,600 per one IVF cycle.

Study variables

The binary outcome variable was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The clinical pregnancy rate was calculated per egg retrieval cycle (cumulatively from fertilized fresh and frozen eggs). Patients were followed up for three months after an embryo(s) transfer. Patients with "unknown" status were those who have not yet reached 8 weeks gestation and have not yet had an ultrasound to determine the presence or absence of clinical pregnancy. Patients provided socio-demographic data such as age in years, body mass index (BMI), education level and payment type (publicly funded or self-paid) through a survey. BMI was categorized as underweight (less than 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and overweight/obese (25 kg/m^2 and above). According to the International Standard Classification of Education (ISCED), education level was grouped to ISCED 4 level—secondary high school, ISCED 5 level—post-secondary non-tertiary education and ISCED 6 level —bachelor or master level education. Patient past medical history data such as comorbidities associated with infertility, duration of infertility, number of previous deliveries, number of previous miscarriages, number of intentional pregnancy interruptions and number of previous IVF cycles were collected using a standardized survey. Clinical data about the number of oocytes retrieved, number of embryos transferred, cause of infertility (female, male and mixed), type of treatment protocol, and multiple pregnancies were collected from patients' medical records.

Statistical analysis

In the descriptive analysis, continuous variables were summarized as means or medians and corresponding variability measurements (standard deviations and inter-quartile ranges). Categorical variables were described in absolute and relative frequencies. To compare means between two-groups, independent t-test or Mann-Whitney U-test was used, where appropriate. To test independence between two categorical variables, the chi-square test or Fisher's exact test was performed. Simple and multiple Poisson regression modeling with robust estimation were

implemented to assess relationships of independent variables with the outcome variable. Since the number of oocytes retrieved is considered a strong predictor for the clinical pregnancy, [18 19] we additionally constructed linear regression models to test associations of independent variables with the number of oocytes retrieved. Models were built according to the parsimonious principle, including a reasonable number of covariates based on their clinical, epidemiological importance and statistical significance. We hypothesized that the payment type and clinical setting would be highly associated, and inclusion both would result in multicollinearity. However, no multicollinearity was observed. To check multicollinearity, we utilized the variance inflation factor and examined changes in coefficients and its standard errors by adding and removing these variables from the models. We decided to include both variables in the regression modeling as private clinics look for additional income by treating publicly funded patients, likewise, public clinics are encouraged to provide out-of-pocket services. No interaction was observed between payment type and clinical setting at significance level of 0.05. Nonetheless, we presented results from the model with the interaction between clinical settings and payment type, as it was practically important to see whether the outcomes differ between private and public clinics depending on payment type. We also checked for other interactions. An interaction between comorbidity and the clinical settings was found statistically significant. Lastly, we examined the goodness-of-fit of the final models using Pearson's and deviance goodness-of-fit tests. The goodness-of-fit statistics were non-significant, indicating that the models fitted well enough to the sample data.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Four hundred forty-six women attending IVF clinics agreed to participate in the study. The average age of the participants was 33.8±5.6 years (Table 1). One-third of women were overweight or obese (27.9%), approximately half of them had education level at ISCED 6 (45.1%), and two-thirds paid themselves (out-of-pocket) for IVF treatment (67.9%). On average, infertility duration was 5.9±3.9 years (Table 2). A female factor as a cause of infertility was determined in half of the women, while in others factor was mixed or male, and a quarter of the women had previously attempted at least one IVF cycle treatment (24.2%). Most women were treated with short or long classic protocol, and the cumulative pregnancy rate reached 62.2% (Table 3).

Table 1. Socio-demographic characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Age (years), mean±SD	33.8±5.6	33.9±4.9	33.7±5.9	0.81
Missing data=2%				
BMI, n (%)				
Underweight	44 (11.0)	10 (7.3%)	34 (12.9%)	<0.01
Normal	245 (61.1)	76 (55.5%)	169 (64.0%)	
Overweight/Obese	112 (27.9)	51 (37.2%)	61 (23.1%)	
Missing data=10%				
Education level, n (%)				
ISCED 4	120 (27.0%)	51 (36.4%)	69 (22.7%)	<0.01
ISCED 5	124 (27.9%)	26 (18.6%)	98 (32.2%)	

ISCED 6	200 (45.1%)	63 (45.0%)	137 (45.1%)	
Missing data=0.5%				
Location, n (%)				
Aktobe	67 (15.0%)	67 (47.2%)	0 (0%)	
Almaty	99 (22.2%)	0 (0%)	99 (32.6%)	
Nur-Sultan	183 (41.0%)	75 (52.8%)	108 (35.5%)	
Shymkent	97 (21.8%)	0 (0%)	97 (31.9%)	
Missing data=0%				
Payment type, n (%)				
Publicly funded	112 (32.1%)	85 (59.9%)	27 (13.0%)	<0.001
Self-paid	237 (67.9%)	57 (40.1%)	180 (87.0%)	
Missing data=21.8%				

Table 2. Past IVF medical history of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Comorbidity, n (%)				
Yes	174 (39.0%)	83 (58.4%)	91 (29.9%)	<0.001
No	272 (61.0%)	59 (41.6%)	213 (70.1%)	
Missing data=0%				
Infertility duration (years)				
Mean±SD	5.9±3.9	6.0±3.5	5.9±4.1	0.75
Median (IQR)	5 (3-8)	6 (3-8)	5 (3-8)	
Missing data=5.6%				
Number of previous deliveries, n (%)				
None	298 (67.1%)	106 (74.6%)	192 (63.6%)	<0.001
One	112 (25.2%)	36 (25.4%)	76 (25.2%)	
2 or more	34 (7.7%)	0 (0%)	34 (11.2%)	
Missing data=0.5%				
Number of previous miscarriages, n (%)				
None	384 (86.5%)	127 (89.4%)	257 (85.1%)	0.21
One or more	60 (13.5%)	15 (10.6%)	45 (14.9%)	
Missing data=0.5%				
Number of previous intentional pregnancy interruptions, n (%)				
None	404 (91.0%)	125 (88.0%)	279 (92.4%)	0.14
One or more	40 (9.0%)	17 (12.0%)	23 (7.6%)	
Missing data=0.5%				
Number of previous IVF cycles, n (%)				
None	335 (75.8%)	106 (75.2%)	229 (76.1%)	0.41
One	67 (15.2%)	25 (17.7%)	42 (13.9%)	
2 or more	40 (9.0%)	10 (7.1%)	30 (10.0%)	
Missing data=0.9%				
Cause of infertility, n (%)				
Female	218 (49.3%)	57 (40.4%)	161 (53.5%)	<0.01
Male	41 (9.3%)	8 (5.7%)	33 (11.0%)	
Mixed	183 (41.4%)	76 (53.9%)	107 (35.5%)	
Missing data=0.9%				

Table 3. Clinical IVF characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Number of oocytes retrieved				
Mean±SD	10.5±2.0	8.1±7.2	11.5±8.4	<0.001
Median (IQR)	1 (0-2)			
Missing data=9%				
Number of embryos transferred				
Mean±SD	2.0±2.2	1.4±1.1	2.2±2.5	<0.001
Median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	
Missing data=14.8%				
Used protocol				
Classic-long	36 (8.3%)	5 (3.7%)	31 (10.3%)	0.06
Classic-short	379 (86.9%)	122 (90.4%)	257 (85.4%)	

Non-classic – natural cycle	7 (1.6%)	2 (1.5%)	5 (1.7%)	
Non-classic – ultrashort	13 (3.0%)	5 (3.75)	8 (2.7%)	
Non-classic – stimulated in luteal phase	1 (0.2%)	1 (0.7%)	0 (0%)	
Missing data=2.2%				
Clinical pregnancy, n (%)				
Yes	216 (62.2%)	35 (29.7%)	181 (79.0%)	<0.001
No	131 (37.8%)	83 (70.3%)	48 (21.0%)	
Missing data=22.2%				
Clinical pregnancy rate per embryos transferred, %	38.3	22.0	44.7	<0.01
Missing data=22.2%				
Multiple pregnancies, n (%)				
Yes	4 (1.0%)	0 (0%)	4 (1.4%)	0.32
No	418 (99.0%)	131 (100%)	287 (98.6%)	
Missing data=5%				

Public vs private clinics.

More than two-thirds of women attended private clinics (68.2%). There were no differences in age (p=0.81), infertility duration (p=0.75), number of previous miscarriages (p=0.21), number of previous intentional pregnancy interruptions (0.14), and number of previous IVF cycles (p=0.41) between participants of public and private clinics (Table 2). Public clinics had statistically significantly higher proportions of overweight or obese women (p<0.01), patients with education level at ISCED 4 (p<0.01) and patients who were publicly funded (p<0.001) than private clinics. The proportion of patients with comorbidities was also higher in public clinics (58.4% vs 29.9%, p<0.001) than in private clinics. However, the percentage of women with a history of previous deliveries (p<0.001) and the proportion of patients who had a female factor as a cause of infertility (p<0.01) were statistically significantly higher among patients in private clinics. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had more multiple pregnancies (0 vs 4, p=0.32) than public clinics (Table 3). Private clinics had a statistically significantly higher cumulative pregnancy rate (79.0% vs 29.7%, p<0.001) and higher clinical pregnancy rate per embryos transferred (44.7% vs 22.0%, p<0.01) compared to public clinics.

Publicly funded vs self-paid

One-third of women (32.1%) received public funding for IVF treatment. There was no difference between publicly funded and self-paid patients in terms of age, BMI, comorbidity, number of previous miscarriages and number of previous intentional pregnancy interruptions (Supplementary Tables 1-2). Despite that the number of oocytes retrieved, the number of embryos transferred, and type of treatment protocol used were comparable in the two groups, cumulative clinical pregnancy rates were statistically significantly different between them (53.1% vs 65.2%, p=0.04, publicly funded vs self-paid, respectively, Supplementary Table 3).

Factors associated with IVF outcomes.

In bivariable analysis, clinical pregnancy was statistically significantly associated with BMI, education level, location, type of payment, history of comorbidity, number of previous IVF cycles and number of oocytes retrieved during IVF treatment (Supplementary Tables 4-6).

Table 4. Simple and multiple Linear and Poisson regression analyses of clinical settings and payment type predicting the number of oocytes retrieved and IVF clinical pregnancy.

	Number of oocytes retrieved		Clinical pregnancy	
	Crude β-coefficient (95% CI)	†Adjusted β-coefficient (95% CI)	Crude RR (95% CI)	&Adjusted RR (95% CI)
	Model 1		Model 3	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-3.7 (-5.5; 1.9)	0.38 (0.26; 0.54)*	0.44 (0.33; 0.59)*
	Model 2		Model 4	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-5.6 (-7.8; -3.4)*	0.38 (0.26; 0.54)*	0.39 (0.29; 0.52)*
Self-paid	Reference	Reference	Reference	Reference
Publicly funded	-0.2 (-2.0; 1.7)	3.3 (1.1; 5.5)*	0.82 (0.59; 1.12)	1.23 (1.02; 1.47)*

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles

& Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

RR = relative risk, CI = confidence interval.

Table 5. The relationship of clinical settings modified by the funding model with the number of oocytes retrieved and IVF clinical pregnancy using multiple Linear and Poisson regression analyses.

	†Adjusted β-coefficient (95% CI) for number of oocytes retrieved		p-value	&Adjusted RR (95% CI) for clinical pregnancy		p-value
	Publicly funded	Self-paid		Publicly funded	Self-paid	
Private clinics	Reference	Reference	0.10	Reference	Reference	0.19
Public clinics	-3.31 (-6.81; 0.19)	-6.86 (-9.49; -4.22)		0.46 (0.33; 0.64)	0.30 (0.17; 0.54)	

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles

& The model was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

RR = relative risk, CI = confidence interval, p-values are calculated for interaction terms.

Public clinics on average retrieved a lower number of oocytes than private clinics (estimated β-coefficient= -5.6, 95% CI -7.8; -3.4) controlling for payment type and other covariates (Table 4). While adjusting for the number of oocytes retrieved, the number of embryos transferred and payment type, IVF procedures in public clinics were independently negatively associated with the clinical pregnancy (RR=0.39, 95% CI 0.29; 0.52). Women who were publicly funded for IVF treatment had on average a higher number of oocytes retrieved (estimated β-coefficient=3.3, 95% CI 1.1; 5.5) and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95% CI 1.02; 1.47) than those who were self-paid in the multiple regression models.

Even though the relationship between clinical settings and the IVF clinical pregnancy rate was not modified by the payment type (p=0.19), we noticed that women who paid out of pocket had a

stronger negative association with the IVF clinical pregnancy rate (and had a relatively lower number of oocytes retrieved) than patients who were publicly funded, among women who attended public clinics (Table 5). There was, additionally, a statistically significant interaction between clinical settings and comorbidity in predicting IVF clinical pregnancy. The adjusted relative risk of clinical pregnancy between public clinics vs private clinics among patients with no history of comorbidities was 0.72 (0.54; 0.95), while among those with a history of at least one comorbidity was 0.13 (0.07; 0.26) adjusted for covariates.

Discussion

This is the first multicenter study conducted comparing IVF outcomes between private and public clinics in Kazakhstan. The study results show that the private clinics had a significantly higher clinical pregnancy rate. This difference could be partially explained by the more rigorous selection of subfertile women with better IVF prognosis in private clinics. Indeed, our study results confirm it: the private clinics had a lower percentage of overweight or obese women and a lower proportion of women with comorbidities than public clinics. Previous studies have shown that higher BMI levels and infertility-related comorbidities were negatively predictive of IVF outcomes.[18 20] In addition, the private clinics retrieved and transferred a statistically significantly higher number of oocytes and embryos, respectively. A systematic review and meta-analysis by Van Loendersloot et al illustrated that a higher number of oocytes retrieved, and a higher number of embryos transferred were positively associated with successful IVF outcomes.[18] As treatment costs per an IVF cycle are high, patients in private clinics want to maximize the likelihood to conceive a child by retrieving and transferring more oocytes and embryos in a given IVF cycle.[21] However, transferring more embryos is associated with multiple gestation pregnancies.[22] Indeed, our study results found that all multiple gestation pregnancies occurred among women attending private clinics. Multiple gestation pregnancies are not only associated with higher risks of morbidity and mortality for mothers during pregnancy,[23] but also with greater total pregnancy costs, antenatal care and delivery costs when compared with singleton births.[24] Introduction of insurance coverage or public funding of reproductive treatment in many countries has resulted in the reduction of the number of embryos transferred per cycle, consequently, decreased incidence rates of multiple pregnancies[21 25 26] and reduced associated healthcare and patient costs.

After controlling for covariates, patients in public clinics still were less likely to conceive a child than patients in private clinics. Independent from the number of oocytes retrieved and number of embryos transferred, public clinics had lower clinical pregnancy rates. To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 7). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[16] The sensitivity analysis revealed that the public clinics were still independently associated with lower clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates.

Given that we controlled for important confounding variables in the models, lower pregnancy rates in public clinics could be potentially attributed to other factors. For example, patients with higher socioeconomic status are likely to choose private clinics. Previous studies have shown that patients from poor socioeconomic communities had lower levels of anti-Mullerian hormone and antral follicle count, indicating reduced ovarian reserve and a lower probability of conceiving a child.[27] Also, several studies have suggested that a "physician factor" is an important predictor of successful IVF outcomes[28] align with the number of oocytes retrieved,[29] number of high-quality embryos transferred and absence of blood or mucus on the transfer catheter.[30] Lastly, private clinics potentially continuously update their equipment to provide advanced and high-technology care. Latest technologies foster patient-centered care by allowing more data collection that can be used for personalized and more effective IVF treatment.

Based on previous studies, we expected that publicly funded women would have a lower pregnancy rate than women who self-paid because public funding eliminates barriers related to treatment costs and encourages women with worse prognoses to seek IVF treatment.[21 25 26] However, public funding is not widely available in Kazakhstan and only a small percentage of subfertile women receive funding. Thus, those who are selected to receive state funding usually have a higher probability of conceiving a child.[31] Indeed, our study results showed that publicly funded women had a higher likelihood of conceiving a child than self-paid women. Bureaucratic barriers, in addition, discourage financially disadvantaged patients from applying for public funding and seeking IVF treatment. While financially independent patients who do not meet public funding criteria – because of their worse reproductive prognosis – seek IVF treatment by paying out-of-pocket. This speculation is supported by the findings from the multiple linear regression modeling factors associated with the number of oocytes retrieved. In the linear model, independent from other factors, patients who were publicly funded had a higher number of oocytes retrieved than self-paid women which indicates that self-paid patients had reduced ovarian reserve, thus, the lower probability to become pregnant.[19] It is likely that when public funding becomes more widely available in Kazakhstan, the utilization of IVF services will increase and not only women with better reproductive prognoses will access IVF treatment, but also patients with poor prognosis. Thus, the relative number of women with poor reproductive prognoses is expected to proportionally increase.[32] Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.[33]

Since government-funded IVF cycles can be performed in both clinical settings as the government encourages the private sector to provide health care services under the governmental support and similarly, the public sector is stimulated to provide services on a self-paid basis, it was of the study interest to investigate the interaction between clinical settings and funding type in predicting the IVF outcome. Despite that the interaction between clinical setting and payment type was not statistically significant, we found that among self-paid women attending public clinics had a stronger negative association with IVF outcomes (relatively lower number of oocytes retrieved and lower clinical pregnancy rates) than among women who were publicly funded. There is a need to conduct further studies to investigate the existence of the interaction between the clinical settings and payment type among IVF patients. Also, we found that patients with a history of at least one comorbidity and attending public clinics had the lowest probability of conceiving a child. Patients with more severe comorbidities likely undergo IVF cycles in public clinics because they might have been refused to be treated in private clinics – the more rigorous selection process of subfertile women with better IVF prognosis is in place. Previous studies have shown that medical comorbidities were negatively associated with IVF pregnancy rates.[34 35] However, none of the studies examined the effect modification of medical comorbidities on the relationship between clinical setting and IVF outcomes.

Strengths and limitations

This is the first multicenter study investigating IVF clinical pregnancy rates between private and public clinical settings and between self-paid and publicly funded subfertile patients in Kazakhstan. The multivariable analysis that included clinically and epidemiologically important variables in the models allowed us to examine independent relationships of the clinical settings and payment type with the IVF outcomes.

Several study limitations that should be mentioned. First, non-response bias could be present as the response rate was very low (14%). Since descriptive data on non-respondents were not collected for comparison, we were not able to confirm or exclude non-response bias. Overall, given the low response rate, the generalizability of the study results should be considered with caution. Second, 22% of the study participants had missing IVF outcome data. The associations of the IVF outcomes with clinical settings could be overestimated, as women with unknown IVF outcomes, who were not included in the multivariable analysis, had poor prognosis (were likely overweight or obese, had the longest infertility duration and a higher proportion of those who previously attempted IVF cycles).[36] Third, other important variables that could potentially confound the relationships were not collected. Although we controlled for several covariates in the models, inclusion of additional variables (behavioral factors such as smoking, alcohol consumption, physical activity; environmental factors; parental demographical characteristics; embryo quality; experience and qualification of physicians; and number of times embryos transfers were performed within one egg retrieval cycle) could benefit future research in obtaining less biased results. Last, the small sample size in the regression models did not allow to obtain more robust estimates of the associations of clinical settings and payment type with IVF clinical pregnancy.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. Private clinics had a lower proportion of overweight or obese women and a lower proportion of women with comorbidities than public clinics. Private clinics retrieved, on average, higher number of oocytes and had higher multiple gestation pregnancy rate than public clinics. Women with better prognosis were likely selected to receive the IVF treatment through public funding, as the demand is high in Kazakhstan. There is a need to further investigate whether the increase in public funding would influence clinical pregnancy rates among subfertile women.

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Contributors

GB and MT conceived the study. AI and MT contributed to the study design. GA, ST, TU, SB, AA, GU, ZD, GBe, and AB contributed to the acquisition of data. AI, MT, and GA contributed to data analysis and have verified the underlying data. AI, GA, and ST contributed to the initial drafting of the manuscript. GA, GB, TU, SB, AB, and MT contributed to study supervision. AI, GA, and MT contributed to reviewing and finalizing the manuscript. All authors approved the final version of the report and agree to be accountable for all aspects of the work.

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Competing interests

SB is a paid employee of Ecomed IVF private clinic.

Patient consent for publication

Not required.

Ethics statement

The University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee(#120/28012019)

Data availability statement

Data can be requested from the corresponding author.

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Supplementary Tables

Supplementary Table 1. Socio-demographic characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Age (years), mean±SD	34.2±4.8	34.2±5.9	0.99	32.1±5.7
BMI, n(%)				
Underweight	12 (10.8%)	32 (13.9%)	0.62	0 (0%)
Normal	69 (62.2%)	132 (57.1%)		44 (74.6%)
Overweight/Obese	30 (27.0%)	67 (29.0%)		15 (25.4%)
Education level, n(%)				
ISCED 4	39 (34.8%)	47 (20.0%)	<0.01	34 (35.1%)
ISCED 5	27 (24.1%)	90 (38.3%)		7 (7.2%)
ISCED 6	46 (41.1%)	98 (41.7%)		57.7%)
Location, n(%)				
Aktobe	41 (36.6%)	26 (11.0%)	<0.001	0 (0%)
Almaty	3 (2.7%)	96 (40.5%)		0 (0%)
Nur-Sultan	68 (60.7%)	115 (48.5%)		0 (0%)
Shymkent	0 (0%)	0 (0%)		97 (100%)

Supplementary Table 2. Past and current medical history of infertility of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Comorbidity, n(%)				
Yes	49 (43.7%)	125 (52.7%)	0.12	0 (0%)
No	63 (56.3%)	112 (47.3%)		97 (100%)
Infertility duration (years)				
Mean±SD	6.6±3.6	5.1±3.9	<0.01	7.0±3.9
Median (IQR)	6 (4-8)	4 (3-7)		6 (4-9.5)
Number of previous deliveries, n(%)				
None	87 (77.7%)	150 (63.5%)	<0.01	61 (63.5%)
One	24 (21.4%)	62 (26.3%)		26 (27.1%)
Two or more	1 (0.9%)	24 (10.2%)		9 (9.4%)
Number of previous miscarriages, n(%)				
None	100 (89.3%)	205 (86.9%)	0.52	79 (82.3%)
One or more	12 (10.7%)	31 (13.1%)		17 (17.7%)
Number of previous intentional pregnancy interruptions, n(%)				
None	101 (90.2%)	209 (88.6%)	0.65	94 (97.9%)
One or more	11 (9.8%)	27 (11.4%)		2 (2.1%)
Number of previous IVF cycles, n(%)				
None	84 (75.7%)	184 (78.6%)	0.03	67 (69.1%)
One	20 (18.0%)	22 (9.4%)		25 (25.8%)
2 or more	7 (6.3%)	28 (12.0%)		5 (5.1%)
Cause of infertility, n(%)				
Female	35 (31.2%)	106 (45.3%)	<0.01	77 (80.2%)
Male	6 (5.4%)	22 (9.4%)		13 (13.5%)
Mixed	71 (63.4%)	106 (45.3%)		6 (6.3%)

Supplementary Table 3. IVF treatment characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Number of oocytes retrieved				
Mean±SD	10.2±8.0	10.3±8.1	0.87	11.2±8.8
Median (IQR)	9 (4-14)	9 (4-14)		9 (4-14)
Number of embryos transferred				
Mean±SD	1.6±1.0	1.5±0.8	0.93	4.5±4.8
Median (IQR)	2 (1-2)	2 (1-2)		2 (1-6)
Used protocol, n(%)				
Classic-long	7 (6.6%)	28 (12.0%)	0.09	1 (1.0%)
Classic-short	94 (89.5%)	189 (80.8%)		96 (99.0%)
Non-classic – natural cycle	2 (1.9%)	5 (2.1%)		0 (0%)
Non-classic – ultrashort	1 (1.0%)	12 (5.1%		0 (0%)
Non-classic – stimulated in luteal phase	1 (1.0%)	0 (0%)		0 (0%)
Clinical pregnancy, n (%)				
Yes	51 (53.1%)	146 (65.2%)	0.04	19 (70.4%)
No	45 (46.9%)	78 (34.8%)		8 (29.6%)
Miscarriage, n(%)				
Yes	0 (0%)	1 (0.4%)	1.00	0 (0%)
No	102 (100%)	225 (99.6%)		24 (100%)
Multiple pregnancies, n(%)				
Yes	1 (1.0%)	3 (1.3%)	1.00	0 (0%)
No	103 (99.0%)	226 (98.7%)		89 (100%)

Supplementary Table 4. Socio-demographic characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Age (years), mean±SD	33.7±5.9	34.5±5.2	0.21	33.0
BMI, n(%)				
Underweight	38 (18.2%)	4 (3.2%)	<0.001	2 (3.0%)
Normal	130 (62.2%)	74 (58.7%)		41 (62.1%)
Overweight/Obese	41 (19.6%)	48 (38.1%)		23 (34.9%)
Education level, n(%)				
ISCED 4	49 (38.0%)	40 (18.5%)	<0.001	31 (31.3%)
ISCED 5	30 (23.3%)	81 (37.5%)		13 (13.1%)
ISCED 6	50 (38.7%)	95 (44.0%)		55 (55.6%)
Location, n(%)				
Aktobe	31 (23.7%)	26 (12.0%)	0.02	10 (10.1%)
Almaty	38 (29.0%)	59 (27.3%)		2 (2.0%)
Nur-Sultan	54 (41.2%)	112 (51.9%)		17 (17.2%)
Shymkent	8 (6.1%)	19 (8.8%)		70 (70.7%)
Type of payment, n(%)				
State-funded	51 (25.9%)	45 (36.6%)	0.04	16 (55.2%)
Self-paid	146 (74.1%)	78 (63.4%)		13 (44.8%)

Supplementary Table 5. Past and current medical history of infertility of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Comorbidity, n(%)				
Yes	76 (35.2%)	80 (61.1%)	<0.001	18 (18.2%)
No	140 (64.8%)	51 (38.9%)		81 (81.8%)
Infertility duration (years)				
Mean±SD	5.4±3.7	6.1±4.0	0.13	6.7±3.9
Median (IQR)	4.8 (3-7)	5 (3-8)		6.5 (4-9)
Number of previous deliveries, n(%)				
None	144 (66.7%)	90 (69.2%)	0.29	64 (65.3%)
One	50 (23.1%)	33 (25.4%)		29 (29.6%)
Two or more	22 (10.2%)	7 (5.4%)		5 (5.1%)
Number of previous miscarriages, n(%)				
None	190 (88.0%)	111 (85.4%)	0.49	83 (84.7%)
One or more	26 (12.0%)	19 (14.6%)		15 (15.3%)
Number of previous intentional pregnancy interruptions, n(%)				
None	198 (91.7%)	116 (89.2%)	0.45	90 (91.8%)
One or more	18 (8.3%)	14 (10.8%)		8 (8.2%)
Number of previous IVF cycles, n(%)				
None	179 (83.4%)	90 (68.7%)	<0.01	66 (68.7%)
One	18 (8.4%)	26 (19.8%)		23 (24.0%)
2 or more	18 (8.4%)	15 (11.5%)		7 (7.3%)
Cause of infertility, n(%)				
Female	97 (45.1%)	55 (42.3%)	0.32	66 (68.0%)
Male	16 (7.4%)	16 (12.3%)		9 (9.3%)
Mixed	102 (47.4%)	59 (45.4%)		22 (22.7%)

Supplementary Table 6. IVF treatment characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Number of oocytes retrieved				
Mean±SD	11.2±7.8	8.5±7.9	<0.01	11.6±9.4
Median (IQR)	10 (6-14)	7 (2-13)		6 (4-17)
Number of embryos transferred				
Mean±SD	1.7±0.8	1.7±1.9	0.10	4.7±4.9
Median (IQR)	2 (1-2)	1 (1-2)		2 (1-6.5)
Used protocol, n(%)				
Classic-long	23 (10.7%)	11 (8.4%)	0.27	2 (2.2%)
Classic-short	177 (82.3%)	114 (87.0%)		88 (97.8%)
Non-classic – natural cycle	4 (1.9%)	3 (2.3%)		0 (0%)
Non-classic – ultrashort	11 (5.1%)	2 (1.5%)		0 (0%)
Non-classic – stimulated in luteal phase	0 (0%)	1 (0.8%)		0 (0%)

Supplementary Table 7. Simple and multiple Poisson regression analyses of clinical setting and payment type predicting IVF clinical pregnancy (sensitivity analysis, excluding women from Astana private clinic (n=108) with the highest pregnancy rate).

Scales	**Clinical pregnancy**	
	Crude RR (95% CI)	**[&]Adjusted RR (95% CI)**
		Model A
Public clinics	0.47 (0.32; 0.70)*	0.54 (0.39; 0.75)*
		Model B
Public clinics	0.47 (0.32; 0.70)*	0.43 (0.27; 0.69)*
Publicly funded	0.80 (0.51; 1.25)	1.44 (0.90; 2.32)
	Model C **[&]Adjusted RR (95% CI)**	
	Publicly funded	Self-paid
Public clinics	0.87 (0.32; 2.34)	0.34 (0.19; 0.63)

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl. Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

Running title: **Utilization of governmental support of IVF procedures**

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Abstract

Objectives

Infertility rates have been increasing in low- and middle-income countries, including Kazakhstan. The need for accessible and affordable assisted reproductive technologies has become essential for many subfertile women. We aimed to explore whether the public funding and clinical settings are independently associated with IVF clinical pregnancy and to determine whether the relationship between IVF clinical pregnancy and clinical settings is modified by payment type.

Design

A prospective cohort study

Setting

Three private and two public IVF clinics located in major cities

Participants

Women aged ≥ 18 seeking first or repeated IVF treatment and agreed to complete a survey were included in the study. Demographical and past medical history data were collected from a survey, while clinical data from medical records. The total response rate was 14%.

Primary and secondary outcome measures

Clinical pregnancy was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The outcome data were missing for 22% of women.

Results

Out of 446 women in the study, 68.2% attended private clinics. Two-thirds of women attending public clinics and 13% of women attending private clinics were publicly funded. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), and transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had a statistically significantly higher pregnancy rate compared to public clinics (79.0% vs 29.7%, p<0.001). Publicly-funded women had on average a higher number of oocytes retrieved and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95%CI 1.02; 1.47) than self-paid women, after adjusting for covariates. There was no statistically significant interaction between clinical setting and payment type.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. There is also a need to further investigate whether the increase in public funding will influence clinical pregnancy rates.

Key words: Governmental support, financial support, utilization, Infertility; IVF treatment; Stress; Depression; Anxiety; Kazakhstan

Strengths and limitations of this study

This is the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings in Kazakhstan.

Non-response bias may result in overestimation of the association between clinical settings and funding models with the IVF outcome because it is possible that non-respondents had a more likely poor prognosis.

22% of the study participants had unknown IVF outcomes and were excluded from the multivariable analysis.

Although we controlled for several covariates in the models, inclusion of additional variables such as behavioral, environmental factors, parental demographical characteristics, embryo quality, and other factors could benefit future research in obtaining less biased results.

Introduction

Infertility is defined as an inability to conceive within 12 months of an unprotected sexual intercourse in women younger than 35 years or within 6 months in women older than 35 years.[1 2] Infertility affects a significant proportion of the population around the globe, and it is estimated to affect between 8% and 12% of reproductive-aged couples worldwide. [3-5] However, in some developing countries, the rates of infertility are much higher, reaching 25-30% in some populations.[3] It is estimated that more than 180 million couples in developing countries suffer from primary or secondary infertility.[6] Taking into consideration that the desire for parenthood is one of the basic human needs and rights, the worldwide infertility problem becomes even more dramatic. In most societies, despite cultural or religious preferences, becoming a parent is perceived as an essential component in achieving self-realization and meaning in life.[7]

One of the most important issues in contemporary assisted reproductive technologies (ART) markets is access to the treatment.[8 9] As infertility is a medical condition, and couples with unfavorable fertility characteristics should have equal access to receive medical care. Currently in many countries, healthcare policymakers are trying to increase access to ART treatment for patients who cannot afford to pay out of pocket for the treatment.[8] Moreover, the relative cost that patients pay for ART treatment predicts not only the level of access but also the number of embryos transferred.[9] This fact makes insurance or governmental support is very important. There is a huge demand and unmet need for ART, especially in developing countries with a high infertility rate.[6] A health economic report in 2002 put the lowest estimate of the global need for ART at 1,500 cycles per million populations per year, assuming that only 50% of couples who need ART will have it done.[10] At the same time, there is a large difference in both infertility services availability and quality between high- and low-income countries and between the rich and the poor within the same country,[11] particularly in ART procedures, which violates the basic ethical principles of justice, equity and equality.[8 11 12] However, some studies showed that insurance support to ART access can lead to a substantial increase in in vitro fertilization (IVF) usage in a market, [8] therefore, controlling by specific patient selection is required. This will ensure that the treatment for couples with severe medical needs will be available.

Despite an increasing medical demand for infertility treatments, public funding challenges for IVF exist in many developing countries.[13] While high-income countries like France, Spain, and Israel, provide full coverage of IVF treatments as a part of social policy, low-income countries cannot afford it. In the situation when coverage for IVF is absent or incomplete, it makes the IVF treatments unaffordable for couples with the most need. From both the public health and economic standpoint, the financial support of IVF may represent a good investment in terms of governmental financial returns, even in lower-income countries with state-financed health care systems such as Ukraine, Belarus, and Kazakhstan.[13] There is an interest to support IVF treatments from a governmental perspective. After successful IVF treatment, subfertile couples give births to new citizens who will eventually become future taxpayers. However, access to IVF is dependent not only on the particular country income but also on the efficiency of wealth distribution, and the health policy, and health insurance system.[8 13]

Kazakhstan is a developing Central Asian republic, and one of the countries with the highest regional infertility prevalence.[3 13-16] Fertility as a cornerstone of family planning in Central Asian culture plays an important role in the strength of couples' relationships.[16] However, the fertility rate in Kazakhstan decreased significantly from 4.6 in 1960 to 2.8 in 2015,[15] and the infertility prevalence varies from 12% to 15.5%.[14-16] Considering the infertility issue in Kazakhstan, the need for accessible and affordable ART is found to be very high.

A pioneer clinic for IVF in Kazakhstan was established in 1995 with the first newborn delivered in 1996. The first ART clinic was private, and before 2010 all expenses for IVF treatment had been paid by patients. Since 2010 the Ministry of Healthcare provides funds for IVF coverage, and few public IVF clinics have been established. Apart from public IVF clinics, the public-funded IVF cycles are performed in private clinics as well. Although the funds are limited in amount, from 2010 through 2018 with the governmental support (quotas), around 3,000 babies were born with IVF procedure facilitation. According to the Kazakhstan State Program, in 2021 the government has started funding 7,000 IVF cycles per year.[17] It is 7-times more than in 2020 (1,000 cycles). Considering the mentioned circumstances, it is very important to investigate factors that might have an impact on the IVF outcome and to understand how effectively governmental money has been utilized.

We aimed in this study to investigate the following research questions: "Are public funding and clinical settings independently associated with higher IVF clinical pregnancy rates?" and "Is the relationship between IVF clinical pregnancy and clinical settings modified by payment type?"

Methods

Study design

This prospective cohort study was conducted among women attending ART clinics between June 2019 and September 2020 in Kazakhstan. Women seeking first or repeated IVF treatment were asked to participate in the study, providing them with oral and written informed consent. The response rate was 14% (446 out of 3223). Adult women who were seeking IVF treatment and who were able to answer survey questions in Kazakh, Russian or English were included in the study. Women who were under 18 years old, who were not able to answer the survey questions in Kazakh, Russian or English languages and who refused to provide written informed consent were excluded. The study received ethical approvals from the University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee (#120/28012019).

The study participants were enrolled from three private and two public ART clinics. All private clinics located in major cities are branches of one for-profit medical organization. This private organization was established in 1995 and performed the first IVF treatment in Kazakhstan. The public clinics were also from major cities – the National Research Center of Mother and Child Health (NRCMCH) in Nur-Sultan city and the Regional Perinatal Center in Aktobe city. The hospital-based public clinics have started providing ART treatment starting from 2007 and 2018, respectively. NRCMCH was accredited and certified according to the Joint Commission

International standards. Both private and public clinics are entitled to provide services paid out-of-pocket and under public funding.

IVF treatment is funded through public funding or self-payment (out-of-pocket). Subfertile patients could receive public funding for one IVF cycle per year within the State Guaranteed Health Benefits package of the Republic of Kazakhstan. To receive public funding, women must satisfy several inclusion criteria such as being Kazakhstani residents, being in the age range of 18-42 years old, having a good ovarian reserve, no severe comorbidities that could substantially reduce the probability of conceiving a child via IVF and no children. Women with ovarian or cervical benign or malignant tumors, acute inflammatory diseases, somatic or psychological diseases, and low ovarian reserve do not fall under the government support. Only 15 clinics, five public and ten private, are accredited to provide IVF services under the public funding scheme. On the other hand, self-paid women are not restricted in age, number of IVF cycles per year, or clinical setting where to undergo IVF treatment. For self-paid women, costs associated with IVF treatment range between US$1,200 – US$3,600 per one IVF cycle.

Study variables

The binary outcome variable was clinical pregnancy that was defined as a live intrauterine pregnancy identified by ultrasound scan at eight gestational weeks. The clinical pregnancy rate was calculated per egg retrieval cycle (cumulatively from fertilized fresh and frozen eggs). Patients were followed up for three months after an embryo(s) transfer. Patients with "unknown" status were those who have not yet reached 8 weeks gestation and have not yet had an ultrasound to determine the presence or absence of clinical pregnancy. Patients provided socio-demographic data such as age in years, body mass index (BMI), education level and payment type (publicly funded or self-paid) through a survey. BMI was categorized as underweight (less than 18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and overweight/obese (25 kg/m^2 and above). According to the International Standard Classification of Education (ISCED), education level was grouped to ISCED 4 level—secondary high school, ISCED 5 level—post-secondary non-tertiary education and ISCED 6 level —bachelor or master level education. Patient past medical history data such as comorbidities associated with infertility, duration of infertility, number of previous deliveries, number of previous miscarriages, number of intentional pregnancy interruptions and number of previous IVF cycles were collected using a standardized survey. Clinical data about the number of oocytes retrieved, number of embryos transferred, cause of infertility (female, male and mixed), type of treatment protocol, and multiple pregnancies were collected from patients' medical records.

Statistical analysis

In the descriptive analysis, continuous variables were summarized as means or medians and corresponding variability measurements (standard deviations and inter-quartile ranges). Categorical variables were described in absolute and relative frequencies. To compare means between two-groups, independent t-test or Mann-Whitney U-test was used, where appropriate. To test independence between two categorical variables, the chi-square test or Fisher's exact test was performed. Simple and multiple Poisson regression modeling with robust estimation were

implemented to assess relationships of independent variables with the outcome variable. Since the number of oocytes retrieved is considered a strong predictor for the clinical pregnancy, [18 19] we additionally constructed linear regression models to test associations of independent variables with the number of oocytes retrieved. Models were built according to the parsimonious principle, including a reasonable number of covariates based on their clinical, epidemiological importance and statistical significance. We hypothesized that the payment type and clinical setting would be highly associated, and inclusion both would result in multicollinearity. However, no multicollinearity was observed. To check multicollinearity, we utilized the variance inflation factor and examined changes in coefficients and its standard errors by adding and removing these variables from the models. We decided to include both variables in the regression modeling as private clinics look for additional income by treating publicly funded patients, likewise, public clinics are encouraged to provide out-of-pocket services. No interaction was observed between payment type and clinical setting at significance level of 0.05. Nonetheless, we presented results from the model with the interaction between clinical settings and payment type, as it was practically important to see whether the outcomes differ between private and public clinics depending on payment type. We also checked for other interactions. An interaction between comorbidity and the clinical settings was found statistically significant. Lastly, we examined the goodness-of-fit of the final models using Pearson's and deviance goodness-of-fit tests. The goodness-of-fit statistics were non-significant, indicating that the models fitted well enough to the sample data.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Four hundred forty-six women attending IVF clinics agreed to participate in the study. The average age of the participants was 33.8±5.6 years (Table 1). One-third of women were overweight or obese (27.9%), approximately half of them had education level at ISCED 6 (45.1%), and two-thirds paid themselves (out-of-pocket) for IVF treatment (67.9%). On average, infertility duration was 5.9±3.9 years (Table 2). A female factor as a cause of infertility was determined in half of the women, while in others factor was mixed or male, and a quarter of the women had previously attempted at least one IVF cycle treatment (24.2%). Most women were treated with short or long classic protocol, and the cumulative pregnancy rate reached 62.2% (Table 3).

Table 1. Socio-demographic characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Age (years), mean±SD	33.8±5.6	33.9±4.9	33.7±5.9	0.81
Missing data=2%				
BMI, n (%)				
Underweight	44 (11.0)	10 (7.3%)	34 (12.9%)	<0.01
Normal	245 (61.1)	76 (55.5%)	169 (64.0%)	
Overweight/Obese	112 (27.9)	51 (37.2%)	61 (23.1%)	
Missing data=10%				
Education level, n (%)				
ISCED 4	120 (27.0%)	51 (36.4%)	69 (22.7%)	<0.01
ISCED 5	124 (27.9%)	26 (18.6%)	98 (32.2%)	

ISCED 6	200 (45.1%)	63 (45.0%)	137 (45.1%)	
Missing data=0.5%				
Location, n (%)				
Aktobe	67 (15.0%)	67 (47.2%)	0 (0%)	
Almaty	99 (22.2%)	0 (0%)	99 (32.6%)	
Nur-Sultan	183 (41.0%)	75 (52.8%)	108 (35.5%)	
Shymkent	97 (21.8%)	0 (0%)	97 (31.9%)	
Missing data=0%				
Payment type, n (%)				
Publicly funded	112 (32.1%)	85 (59.9%)	27 (13.0%)	<0.001
Self-paid	237 (67.9%)	57 (40.1%)	180 (87.0%)	
Missing data=21.8%				

Table 2. Past IVF medical history of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Comorbidity, n (%)				
Yes	174 (39.0%)	83 (58.4%)	91 (29.9%)	<0.001
No	272 (61.0%)	59 (41.6%)	213 (70.1%)	
Missing data=0%				
Infertility duration (years)				
Mean±SD	5.9±3.9	6.0±3.5	5.9±4.1	0.75
Median (IQR)	5 (3-8)	6 (3-8)	5 (3-8)	
Missing data=5.6%				
Number of previous deliveries, n (%)				
None	298 (67.1%)	106 (74.6%)	192 (63.6%)	<0.001
One	112 (25.2%)	36 (25.4%)	76 (25.2%)	
2 or more	34 (7.7%)	0 (0%)	34 (11.2%)	
Missing data=0.5%				
Number of previous miscarriages, n (%)				
None	384 (86.5%)	127 (89.4%)	257 (85.1%)	0.21
One or more	60 (13.5%)	15 (10.6%)	45 (14.9%)	
Missing data=0.5%				
Number of previous intentional pregnancy interruptions, n (%)				
None	404 (91.0%)	125 (88.0%)	279 (92.4%)	0.14
One or more	40 (9.0%)	17 (12.0%)	23 (7.6%)	
Missing data=0.5%				
Number of previous IVF cycles, n (%)				
None	335 (75.8%)	106 (75.2%)	229 (76.1%)	0.41
One	67 (15.2%)	25 (17.7%)	42 (13.9%)	
2 or more	40 (9.0%)	10 (7.1%)	30 (10.0%)	
Missing data=0.9%				
Cause of infertility, n (%)				
Female	218 (49.3%)	57 (40.4%)	161 (53.5%)	<0.01
Male	41 (9.3%)	8 (5.7%)	33 (11.0%)	
Mixed	183 (41.4%)	76 (53.9%)	107 (35.5%)	
Missing data=0.9%				

Table 3. Clinical IVF characteristics of the study participants.

Variable	All, N=446 (100%)	Public clinics, n=142 (31.8%)	Private clinics, n=304 (68.2%)	p-value
Number of oocytes retrieved				
Mean±SD	10.5±2.0	8.1±7.2	11.5±8.4	<0.001
Median (IQR)	1 (0-2)			
Missing data=9%				
Number of embryos transferred				
Mean±SD	2.0±2.2	1.4±1.1	2.2±2.5	<0.001
Median (IQR)	2 (1-2)	1 (1-2)	2 (1-2)	
Missing data=14.8%				
Used protocol				
Classic-long	36 (8.3%)	5 (3.7%)	31 (10.3%)	0.06
Classic-short	379 (86.9%)	122 (90.4%)	257 (85.4%)	

Non-classic – natural cycle	7 (1.6%)	2 (1.5%)	5 (1.7%)	
Non-classic – ultrashort	13 (3.0%)	5 (3.75)	8 (2.7%)	
Non-classic – stimulated in luteal phase	1 (0.2%)	1 (0.7%)	0 (0%)	
Missing data=2.2%				
Clinical pregnancy, n (%)				
Yes	216 (62.2%)	35 (29.7%)	181 (79.0%)	<0.001
No	131 (37.8%)	83 (70.3%)	48 (21.0%)	
Missing data=22.2%				
Clinical pregnancy rate per embryos transferred, %	38.3	22.0	44.7	<0.01
Missing data=22.2%				
Multiple pregnancies, n (%)				
Yes	4 (1.0%)	0 (0%)	4 (1.4%)	0.32
No	418 (99.0%)	131 (100%)	287 (98.6%)	
Missing data=5%				

Public vs private clinics.

More than two-thirds of women attended private clinics (68.2%). There were no differences in age (p=0.81), infertility duration (p=0.75), number of previous miscarriages (p=0.21), number of previous intentional pregnancy interruptions (0.14), and number of previous IVF cycles (p=0.41) between participants of public and private clinics (Table 2). Public clinics had statistically significantly higher proportions of overweight or obese women (p<0.01), patients with education level at ISCED 4 (p<0.01) and patients who were publicly funded (p<0.001) than private clinics. The proportion of patients with comorbidities was also higher in public clinics (58.4% vs 29.9%, p<0.001) than in private clinics. However, the percentage of women with a history of previous deliveries (p<0.001) and the proportion of patients who had a female factor as a cause of infertility (p<0.01) were statistically significantly higher among patients in private clinics. Private clinics retrieved, on average, a higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had more multiple pregnancies (0 vs 4, p=0.32) than public clinics (Table 3). Private clinics had a statistically significantly higher cumulative pregnancy rate (79.0% vs 29.7%, p<0.001) and higher clinical pregnancy rate per embryos transferred (44.7% vs 22.0%, p<0.01) compared to public clinics.

Publicly funded vs self-paid

One-third of women (32.1%) received public funding for IVF treatment. There was no difference between publicly funded and self-paid patients in terms of age, BMI, comorbidity, number of previous miscarriages and number of previous intentional pregnancy interruptions (Supplementary Tables 1-2). Despite that the number of oocytes retrieved, the number of embryos transferred, and type of treatment protocol used were comparable in the two groups, cumulative clinical pregnancy rates were statistically significantly different between them (53.1% vs 65.2%, p=0.04, publicly funded vs self-paid, respectively, Supplementary Table 3).

Factors associated with IVF outcomes.

In bivariable analysis, clinical pregnancy was statistically significantly associated with BMI, education level, location, type of payment, history of comorbidity, number of previous IVF cycles and number of oocytes retrieved during IVF treatment (Supplementary Tables 4-6).

Table 4. Simple and multiple Linear and Poisson regression analyses of clinical settings and payment type predicting the number of oocytes retrieved and IVF clinical pregnancy.

	Number of oocytes retrieved		Clinical pregnancy	
	Crude β-coefficient (95% CI)	**†Adjusted β-coefficient (95% CI)**	**Crude RR (95% CI)**	**&Adjusted RR (95% CI)**
	Model 1		Model 3	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-3.7 (-5.5; 1.9)	0.38 (0.26; 0.54)*	0.44 (0.33; 0.59)*
	Model 2		Model 4	
Private clinics	Reference	Reference	Reference	Reference
Public clinics	-3.4 (-5.1; -1.7)	-5.6 (-7.8; -3.4)*	0.38 (0.26; 0.54)*	0.39 (0.29; 0.52)*
Self-paid	Reference	Reference	Reference	Reference
Publicly funded	-0.2 (-2.0; 1.7)	3.3 (1.1; 5.5)*	0.82 (0.59; 1.12)	1.23 (1.02; 1.47)*

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles

& Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

RR = relative risk, CI = confidence interval.

Table 5. The relationship of clinical settings modified by the funding model with the number of oocytes retrieved and IVF clinical pregnancy using multiple Linear and Poisson regression analyses.

	†Adjusted β-coefficient (95% CI) for number of oocytes retrieved		**p-value**	**&Adjusted RR (95% CI) for clinical pregnancy**		**p-value**
	Publicly funded	Self-paid		Publicly funded	Self-paid	
Private clinics	Reference	Reference	0.10	Reference	Reference	0.19
Public clinics	-3.31 (-6.81; 0.19)	-6.86 (-9.49; -4.22)		0.46 (0.33; 0.64)	0.30 (0.17; 0.54)	

† Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, and number of previous IVF cycles

& The model was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

RR = relative risk, CI = confidence interval, p-values are calculated for interaction terms.

Public clinics on average retrieved a lower number of oocytes than private clinics (estimated β-coefficient= -5.6, 95% CI -7.8; -3.4) controlling for payment type and other covariates (Table 4). While adjusting for the number of oocytes retrieved, the number of embryos transferred and payment type, IVF procedures in public clinics were independently negatively associated with the clinical pregnancy (RR=0.39, 95% CI 0.29; 0.52). Women who were publicly funded for IVF treatment had on average a higher number of oocytes retrieved (estimated β-coefficient=3.3, 95% CI 1.1; 5.5) and a statistically significantly higher probability of clinical pregnancy (RR=1.23, 95% CI 1.02; 1.47) than those who were self-paid in the multiple regression models.

Even though the relationship between clinical settings and the IVF clinical pregnancy rate was not modified by the payment type (p=0.19), we noticed that women who paid out of pocket had a

stronger negative association with the IVF clinical pregnancy rate (and had a relatively lower number of oocytes retrieved) than patients who were publicly funded, among women who attended public clinics (Table 5). There was, additionally, a statistically significant interaction between clinical settings and comorbidity in predicting IVF clinical pregnancy. The adjusted relative risk of clinical pregnancy between public clinics vs private clinics among patients with no history of comorbidities was 0.72 (0.54; 0.95), while among those with a history of at least one comorbidity was 0.13 (0.07; 0.26) adjusted for covariates.

Discussion

This is the first multicenter study conducted comparing IVF outcomes between private and public clinics in Kazakhstan. The study results show that the private clinics had a significantly higher clinical pregnancy rate. This difference could be partially explained by the more rigorous selection of subfertile women with better IVF prognosis in private clinics. Indeed, our study results confirm it: the private clinics had a lower percentage of overweight or obese women and a lower proportion of women with comorbidities than public clinics. Previous studies have shown that higher BMI levels and infertility-related comorbidities were negatively predictive of IVF outcomes.[18 20] In addition, the private clinics retrieved and transferred a statistically significantly higher number of oocytes and embryos, respectively. A systematic review and meta-analysis by Van Loendersloot et al illustrated that a higher number of oocytes retrieved, and a higher number of embryos transferred were positively associated with successful IVF outcomes.[18] As treatment costs per an IVF cycle are high, patients in private clinics want to maximize the likelihood to conceive a child by retrieving and transferring more oocytes and embryos in a given IVF cycle.[21] However, transferring more embryos is associated with multiple gestation pregnancies.[22] Indeed, our study results found that all multiple gestation pregnancies occurred among women attending private clinics. Multiple gestation pregnancies are not only associated with higher risks of morbidity and mortality for mothers during pregnancy,[23] but also with greater total pregnancy costs, antenatal care and delivery costs when compared with singleton births.[24] Introduction of insurance coverage or public funding of reproductive treatment in many countries has resulted in the reduction of the number of embryos transferred per cycle, consequently, decreased incidence rates of multiple pregnancies[21 25 26] and reduced associated healthcare and patient costs.

After controlling for covariates, patients in public clinics still were less likely to conceive a child than patients in private clinics. Independent from the number of oocytes retrieved and number of embryos transferred, public clinics had lower clinical pregnancy rates. To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 7). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[16] The sensitivity analysis revealed that the public clinics were still independently associated with lower clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates.

Given that we controlled for important confounding variables in the models, lower pregnancy rates in public clinics could be potentially attributed to other factors. For example, patient's socioeconomic status could be one of them. Patients with lower socioeconomic status are likely to attend public IVF clinics and have poor reproductive prognosis than patients with higher socioeconomic status[27]. Previous studies have shown that patients from poor socioeconomic communities had lower levels of anti-Mullerian hormone and antral follicle count, indicating reduced ovarian reserve and a lower probability of conceiving a child.[28] Also, several studies have suggested that a "physician factor" is an important predictor of successful IVF outcomes[29] align with the number of oocytes retrieved,[30] number of high-quality embryos transferred and absence of blood or mucus on the transfer catheter.[31] Lastly, private clinics potentially continuously update their equipment to provide advanced and high-technology care. Latest technologies foster patient-centered care by allowing more data collection that can be used for personalized and more effective IVF treatment.

Based on previous studies, we expected that publicly funded women would have a lower pregnancy rate than women who self-paid because public funding eliminates barriers related to treatment costs and encourages women with worse prognoses to seek IVF treatment.[21 25 26] However, public funding is not widely available in Kazakhstan and only a small percentage of subfertile women receive funding. Thus, those who are selected to receive state funding usually have a higher probability of conceiving a child.[32] Indeed, our study results showed that publicly funded women had a higher likelihood of conceiving a child than self-paid women. Bureaucratic barriers, in addition, discourage financially disadvantaged patients from applying for public funding and seeking IVF treatment. While financially independent patients who do not meet public funding criteria – because of their worse reproductive prognosis – seek IVF treatment by paying out-of-pocket. This speculation is supported by the findings from the multiple linear regression modeling factors associated with the number of oocytes retrieved. In the linear model, independent from other factors, patients who were publicly funded had a higher number of oocytes retrieved than self-paid women which indicates that self-paid patients had reduced ovarian reserve, thus, the lower probability to become pregnant.[19] It is likely that when public funding becomes more widely available in Kazakhstan, the utilization of IVF services will increase and not only women with better reproductive prognoses will access IVF treatment, but also patients with poor prognosis. Thus, the relative number of women with poor reproductive prognoses is expected to proportionally increase.[33] Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.[34]

Since government-funded IVF cycles can be performed in both clinical settings as the government encourages the private sector to provide health care services under the governmental support and similarly, the public sector is stimulated to provide services on a self-paid basis, it was of the study interest to investigate the interaction between clinical settings and funding type in predicting the IVF outcome. Despite that the interaction between clinical setting and payment type was not statistically significant, we found that among self-paid women attending public clinics had a stronger negative association with IVF outcomes (relatively lower number of oocytes retrieved and lower clinical pregnancy rates) than among women who were publicly funded. There is a need to conduct further studies to investigate the existence of the interaction between the clinical settings and payment type among IVF patients. Also, we found that patients with a history of at least one comorbidity and attending public clinics had the lowest probability of conceiving a child.

Patients with more severe comorbidities likely undergo IVF cycles in public clinics because they might have been refused to be treated in private clinics – the more rigorous selection process of subfertile women with better IVF prognosis is in place. Previous studies have shown that medical comorbidities were negatively associated with IVF pregnancy rates.[35 36] However, none of the studies examined the effect modification of medical comorbidities on the relationship between clinical setting and IVF outcomes.

Strengths and limitations

This is the first multicenter study investigating IVF clinical pregnancy rates between private and public clinical settings and between self-paid and publicly funded subfertile patients in Kazakhstan. The multivariable analysis that included clinically and epidemiologically important variables in the models allowed us to examine independent relationships of the clinical settings and payment type with the IVF outcomes.

Several study limitations that should be mentioned. First, non-response bias could be present as the response rate was very low (14%). Since descriptive data on non-respondents were not collected for comparison, we were not able to confirm or exclude non-response bias. Overall, given the low response rate, the generalizability of the study results should be considered with caution. Second, 22% of the study participants had missing IVF outcome data. The associations of the IVF outcomes with clinical settings could be overestimated, as women with unknown IVF outcomes, who were not included in the multivariable analysis, had poor prognosis (were likely overweight or obese, had the longest infertility duration and a higher proportion of those who previously attempted IVF cycles).[37] Third, other important variables that could potentially confound the relationships were not collected. Although we controlled for several covariates in the models, inclusion of additional variables (behavioral factors such as smoking, alcohol consumption, physical activity; environmental factors; parental demographical characteristics; embryo quality; experience and qualification of physicians; and number of times embryos transfers were performed within one egg retrieval cycle) could benefit future research in obtaining less biased results. Last, the small sample size in the regression models did not allow to obtain more robust estimates of the associations of clinical settings and payment type with IVF clinical pregnancy.

Conclusions

Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. Private clinics had a lower proportion of overweight or obese women and a lower proportion of women with comorbidities than public clinics. Private clinics retrieved, on average, higher number of oocytes and had higher multiple gestation pregnancy rate than public clinics. Women with better prognosis were likely selected to receive the IVF treatment through public funding. There is a need to further investigate what improvements are needed in the public funding sector to increase the clinical pregnancy rates among subfertile women.

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Contributors

GB and MT conceived the study. AI and MT contributed to the study design. GA, ST, TU, SB, AA, GU, ZD, GBe, and AB contributed to the acquisition of data. AI, MT, and GA contributed to data analysis and have verified the underlying data. AI, GA, and ST contributed to the initial drafting of the manuscript. GA, GB, TU, SB, AB, and MT contributed to study supervision. AI, GA, and MT contributed to reviewing and finalizing the manuscript. All authors approved the final version of the report and agree to be accountable for all aspects of the work.

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Competing interests

SB is a paid employee of Ecomed IVF private clinic.

Patient consent for publication

Not required.

Ethics statement

The University Medical Center Institutional Research Ethics Committee (№6/07/06/19) and Nazarbayev University Institutional Research Ethics Committee(#120/28012019)

Data availability statement

Data can be requested from the corresponding author.

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Supplementary Tables

Supplementary Table 1. Socio-demographic characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Age (years), mean±SD	34.2±4.8	34.2±5.9	0.99	32.1±5.7
BMI, n(%)				
Underweight	12 (10.8%)	32 (13.9%)	0.62	0 (0%)
Normal	69 (62.2%)	132 (57.1%)		44 (74.6%)
Overweight/Obese	30 (27.0%)	67 (29.0%)		15 (25.4%)
Education level, n(%)				
ISCED 4	39 (34.8%)	47 (20.0%)	<0.01	34 (35.1%)
ISCED 5	27 (24.1%)	90 (38.3%)		7 (7.2%)
ISCED 6	46 (41.1%)	98 (41.7%)		57.7%)
Location, n(%)				
Aktobe	41 (36.6%)	26 (11.0%)	<0.001	0 (0%)
Almaty	3 (2.7%)	96 (40.5%)		0 (0%)
Nur-Sultan	68 (60.7%)	115 (48.5%)		0 (0%)
Shymkent	0 (0%)	0 (0%)		97 (100%)

Supplementary Table 2. Past and current medical history of infertility of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Comorbidity, n(%)				
Yes	49 (43.7%)	125 (52.7%)	0.12	0 (0%)
No	63 (56.3%)	112 (47.3%)		97 (100%)
Infertility duration (years)				
Mean±SD	6.6±3.6	5.1±3.9	<0.01	7.0±3.9
Median (IQR)	6 (4-8)	4 (3-7)		6 (4-9.5)
Number of previous deliveries, n(%)				
None	87 (77.7%)	150 (63.5%)	<0.01	61 (63.5%)
One	24 (21.4%)	62 (26.3%)		26 (27.1%)
Two or more	1 (0.9%)	24 (10.2%)		9 (9.4%)
Number of previous miscarriages, n(%)				
None	100 (89.3%)	205 (86.9%)	0.52	79 (82.3%)
One or more	12 (10.7%)	31 (13.1%)		17 (17.7%)
Number of previous intentional pregnancy interruptions, n(%)				
None	101 (90.2%)	209 (88.6%)	0.65	94 (97.9%)
One or more	11 (9.8%)	27 (11.4%)		2 (2.1%)
Number of previous IVF cycles, n(%)				
None	84 (75.7%)	184 (78.6%)	0.03	67 (69.1%)
One	20 (18.0%)	22 (9.4%)		25 (25.8%)
2 or more	7 (6.3%)	28 (12.0%)		5 (5.1%)
Cause of infertility, n(%)				
Female	35 (31.2%)	106 (45.3%)	<0.01	77 (80.2%)
Male	6 (5.4%)	22 (9.4%)		13 (13.5%)
Mixed	71 (63.4%)	106 (45.3%)		6 (6.3%)

Supplementary Table 3. IVF treatment characteristics of the study participants by payment type.

Variable	Publicly funded, n=112	Self-paid, n=237	p-value	Unknown, n=97
Number of oocytes retrieved				
Mean±SD	10.2±8.0	10.3±8.1	0.87	11.2±8.8
Median (IQR)	9 (4-14)	9 (4-14)		9 (4-14)
Number of embryos transferred				
Mean±SD	1.6±1.0	1.5±0.8	0.93	4.5±4.8
Median (IQR)	2 (1-2)	2 (1-2)		2 (1-6)
Used protocol, n(%)				
Classic-long	7 (6.6%)	28 (12.0%)	0.09	1 (1.0%)
Classic-short	94 (89.5%)	189 (80.8%)		96 (99.0%)
Non-classic – natural cycle	2 (1.9%)	5 (2.1%)		0 (0%)
Non-classic – ultrashort	1 (1.0%)	12 (5.1%		0 (0%)
Non-classic – stimulated in luteal phase	1 (1.0%)	0 (0%)		0 (0%)
Clinical pregnancy, n (%)				
Yes	51 (53.1%)	146 (65.2%)	0.04	19 (70.4%)
No	45 (46.9%)	78 (34.8%)		8 (29.6%)
Miscarriage, n(%)				
Yes	0 (0%)	1 (0.4%)	1.00	0 (0%)
No	102 (100%)	225 (99.6%)		24 (100%)
Multiple pregnancies, n(%)				
Yes	1 (1.0%)	3 (1.3%)	1.00	0 (0%)
No	103 (99.0%)	226 (98.7%)		89 (100%)

Supplementary Table 4. Socio-demographic characteristics of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Age (years), mean±SD	33.7±5.9	34.5±5.2	0.21	33.0
BMI, n(%)				
Underweight	38 (18.2%)	4 (3.2%)	<0.001	2 (3.0%)
Normal	130 (62.2%)	74 (58.7%)		41 (62.1%)
Overweight/Obese	41 (19.6%)	48 (38.1%)		23 (34.9%)
Education level, n(%)				
ISCED 4	49 (38.0%)	40 (18.5%)	<0.001	31 (31.3%)
ISCED 5	30 (23.3%)	81 (37.5%)		13 (13.1%)
ISCED 6	50 (38.7%)	95 (44.0%)		55 (55.6%)
Location, n(%)				
Aktobe	31 (23.7%)	26 (12.0%)	0.02	10 (10.1%)
Almaty	38 (29.0%)	59 (27.3%)		2 (2.0%)
Nur-Sultan	54 (41.2%)	112 (51.9%)		17 (17.2%)
Shymkent	8 (6.1%)	19 (8.8%)		70 (70.7%)
Type of payment, n(%)				
State-funded	51 (25.9%)	45 (36.6%)	0.04	16 (55.2%)
Self-paid	146 (74.1%)	78 (63.4%)		13 (44.8%)

Supplementary Table 5. Past and current medical history of infertility of the study participants by IVF clinical pregnancy status.

Variable	Pregnant, n=216	Not pregnant, n=131	p-value	Unknown, n=99
Comorbidity, n(%)				
Yes	76 (35.2%)	80 (61.1%)	<0.001	18 (18.2%)
No	140 (64.8%)	51 (38.9%)		81 (81.8%)
Infertility duration (years)				
Mean±SD	5.4±3.7	6.1±4.0	0.13	6.7±3.9
Median (IQR)	4.8 (3-7)	5 (3-8)		6.5 (4-9)
Number of previous deliveries, n(%)				
None	144 (66.7%)	90 (69.2%)	0.29	64 (65.3%)
One	50 (23.1%)	33 (25.4%)		29 (29.6%)
Two or more	22 (10.2%)	7 (5.4%)		5 (5.1%)
Number of previous miscarriages, n(%)				
None	190 (88.0%)	111 (85.4%)	0.49	83 (84.7%)
One or more	26 (12.0%)	19 (14.6%)		15 (15.3%)
Number of previous intentional pregnancy interruptions, n(%)				
None	198 (91.7%)	116 (89.2%)	0.45	90 (91.8%)
One or more	18 (8.3%)	14 (10.8%)		8 (8.2%)
Number of previous IVF cycles, n(%)				
None	179 (83.4%)	90 (68.7%)	<0.01	66 (68.7%)
One	18 (8.4%)	26 (19.8%)		23 (24.0%)
2 or more	18 (8.4%)	15 (11.5%)		7 (7.3%)
Cause of infertility, n(%)				
Female	97 (45.1%)	55 (42.3%)	0.32	66 (68.0%)
Male	16 (7.4%)	16 (12.3%)		9 (9.3%)
Mixed	102 (47.4%)	59 (45.4%)		22 (22.7%)

Supplementary Table 6. IVF treatment characteristics of the study participants by IVF clinical pregnancy status.

Variable	**Pregnant, n=216**	**Not pregnant, n=131**	**p-value**	**Unknown, n=99**
Number of oocytes retrieved				
Mean±SD	11.2±7.8	8.5±7.9	<0.01	11.6±9.4
Median (IQR)	10 (6-14)	7 (2-13)		6 (4-17)
Number of embryos transferred				
Mean±SD	1.7±0.8	1.7±1.9	0.10	4.7±4.9
Median (IQR)	2 (1-2)	1 (1-2)		2 (1-6.5)
Used protocol, n(%)				
Classic-long	23 (10.7%)	11 (8.4%)	0.27	2 (2.2%)
Classic-short	177 (82.3%)	114 (87.0%)		88 (97.8%)
Non-classic – natural cycle	4 (1.9%)	3 (2.3%)		0 (0%)
Non-classic – ultrashort	11 (5.1%)	2 (1.5%)		0 (0%)
Non-classic – stimulated in luteal phase	0 (0%)	1 (0.8%)		0 (0%)

Supplementary Table 7. Simple and multiple Poisson regression analyses of clinical setting and payment type predicting IVF clinical pregnancy (sensitivity analysis, excluding women from Astana private clinic (n=108) with the highest pregnancy rate).

Scales	**Clinical pregnancy**	
	Crude RR (95% CI)	**[&]Adjusted RR (95% CI)**
		Model A
Public clinics	0.47 (0.32; 0.70)*	0.54 (0.39; 0.75)*
		Model B
Public clinics	0.47 (0.32; 0.70)*	0.43 (0.27; 0.69)*
Publicly funded	0.80 (0.51; 1.25)	1.44 (0.90; 2.32)
	Model C **[&]Adjusted RR (95% CI)**	
	Publicly funded	Self-paid
Public clinics	0.87 (0.32; 2.34)	0.34 (0.19; 0.63)

[&] Each of the models was adjusted for age, BMI, education, comorbidity, cause of infertility, infertility duration, number of previous IVF cycles, number of embryos transferred, and number of oocytes retrieved.

*p<0.05

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	12
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7-9
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Suppl. Tables
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.