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Unraveling infertility – most frequent causes and essential predictors of assisted reproductive technologies outcomes

Испитивање неплодности – најчешћи узроци и кључни предиктори исхода поступака асистираних репродуктивних технологија

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Испитивање неплодности – најчешћи узроци и кључни предиктори исхода поступака асистираних репродуктивних технологија

SUMMARY

Introduction/Objective Infertility is a global health concern affecting millions of couples worldwide. The aim of this study was to identify the most common causes of infertility among patients undergoing ART procedures and to determine key predictors of a successful outcome.

Methods This retrospective observational study included 164 patients treated at a University Clinical Center. Patients characteristics – age, body mass index, duration of infertility, baseline hormone levels were recorded, along with stimulation protocol, insemination technique, number of retrieved oocytes, fertilization rate, embryo quality, and treatment outcomes. Univariate and multivariate logistic regression analyses were performed to assess predictors of a clinical pregnancy.

Results The mean age of participants was 34.66 ± 3.69 years, and 89% underwent a short stimulation protocol. Unexplained infertility was most frequent (30.5%), followed by male factor (28.0%). Among the participants, 65.2% had 4–15 retrieved oocytes, while 19.5% had ≤ 3 and 15.2% had > 15. Embryos of quality A were observed in 56.7% of patients. The overall pregnancy rate was 53.7%. Univariate logistic regression identified lower baseline progesterone, higher number of mature oocytes, and better embryo quality as significant predictors of success. In the multivariate model, the number of mature oocytes (p = 0.014) and A-quality embryos (p = 0.004) remained independent predictors of a positive outcome.

Conclusion: This study demonstrates that the number of mature oocytes and top-quality embryos are essential for achieving favorable IVF/ICSI results. Recognizing and addressing these predictive factors may enhance the success rate of assisted reproductive treatments, stressing the need for personalized therapeutic strategies.

Keywords: infertility; ART procedures; embryo quality; progesterone; IVF outcome

САЖЕТАК

Увод/циљ Неплодност представља глобални здравствени проблем који погађа милионе парова широм света. Циљ ове студије био је да идентификује најчешће узроке неплодности код пацијената који се подвргавају асистираним репродуктивним технологијама процедурама и да одреди кључне предикторе успешног исхода.

Методе Ова ретроспективна опсервациона студија обухватила је 164 пацијента лечена у Универзитетском клиничком центру. Карактеристике пацијената биле су: године старости, индекс телесне масе, трајање неплодности, базални хормонски статус, као и протокол стимулације, техника инсеминације, број добијених јајних ћелија, стопа фертилизације, квалитет ембриона и исход лечења. Спроведене су униваријантне и мултиваријантне логистичке регресионе анализе ради процене предиктора клиничких трудноћа.

Резултати Просечна старост испитаница била је 34,66 ± 3,69 година, а 89% је било подвргнуто кратком протоколу стимулације. Најчешћи узрок неплодности била је непоунат фактор (30,5%), затим мушки фактор (28%). Код 65,2% испитаника добијено је између 4 и 15 јајних ћелија, док је 19,5% имало ≤ 3, а 15,2% > 15. Ембриони А-квалитета добијени су код 56,7% пацијенткиња. Укупна стопа трудноће износила је 53,7%. Униваријантна логистичка регресија показала је да су нижи базални ниво прогестерона, већи број зрелих јајних ћелија и бољи квалитет ембриона значајни предиктори успеха. У мултиваријантном моделу, број зрелих јајних ћелија ($p = 0{,}014$) и ембриони А-квалитета ($p = 0{,}004$) остали су независни предиктори позитивног исхода.

Закључак Ова студија показује да су број зрелих јајних ћелија и добар квалитет ембриона од кључне важности за постизање добрих резултата вантелесне оплодње. Препознавање и адекватно управљање овим предиктивним факторима може побољшати успешност асистираних репродуктивних третмана, наглашавајући значај персонализованих терапијских стратегија.

Кључне речи: неплодност; вантелесна оплодња; поступци; квалитет ембриона; прогестерон; исход поступка

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INTRODUCTION

Affecting millions of couples worldwide, infertility becomes a significant global health concern highlighting the need for effective diagnostic and therapeutic strategies [1]. Diverse underlying factors, such as delayed childbearing, baseline levels of reproductive hormones, ovarian reserve, lifestyle habits (e.g., smoking, obesity), and demographic characteristics of the couples have contributed to development of more sophisticated reproductive approaches [2]. According to the report "Women's Health in Serbia – Past, Present and Future," the leading reproductive problems among women in Serbia are menstrual cycle disorders and infertility, alongside a growing need for ART procedures due to the increased prevalence of these conditions [3].

The current increasing evidences about values of BMI, serum progesterone levels and quality of embryos emphasis its potential role on the in Assisted Reproductive Technologies (ART) success [4]. Progesterone, as a key hormone in the luteal phase, plays a crucial role in endometrial preparation and the maintenance of early pregnancy. There are conflicting results about influence of the smoking habits, alcohol consumption, duration of infertility and causes of infertility on IVF outcomes [2, 5], but one is for sure that the success of each procedure depends on the patient's individual clinical presentation, emphasizing the importance of a comprehensive approach that carefully evaluates all relevant predictors. Regarding stimulation protocols, studies suggest that the choice of protocol (e.g., long, short, or antagonist) can influence both the quantity and quality of retrieved oocytes. Similarly, the selection of the insemination technique—IVF, ICSI, or a combined approach—may be critical in cases of severe male factor infertility or varying oocyte quality [6].

Accordingly, the aim of this study was to analyze the characteristics of patients who underwent IVF/ICSI treatment and identifying key predictors of IVF/ICSI success.

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METHODS

A retrospective observational study was conducted at the Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia. All data were analyzed in accordance with ethical principles and research standards. The recruitment of patients was performed in accordance with the Helsinki declaration. All patients were entirely informed about the research and all signed the informed consents for inclusion in the study, as well as the ART itself. The research was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade.

The inclusion criteria encompassed women aged 18 to 40 years undergoing first, second or third ART procedure as independent patients, with a BMI < 30 kg/m², a confirmed infertility diagnosis. Exclusion criteria consisted of azoospermic male partners and female patients who did not meet the inclusion criteria, such as those over 40 years of age or with a BMI exceeding 30 kg/m². Infertility was diagnosed and classified according to the guidelines of the European Society of Human Reproduction and Embryology (ESHRE) [7]. For all patients ultimately included in the study, comprehensive medical histories were obtained, covering the following parameters: demographic characteristics (age, BMI, and duration of infertility), baseline hormonal status (Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and progesterone (P4)), anti-Müllerian hormone (AMH) levels, factor of infertility (male, ovarian, tubal, combined), stimulation protocol (long antagonist or short antagonist protocol), procedure outcomes (number of retrieved oocytes, number of fertilized oocytes, fertilization rate, embryo quality, and pregnancy rate), and pregnancy outcomes (biochemical pregnancy, miscarriage, or live birth).

The stimulation protocols and patient monitoring have been described in detail in a previous study [4]. Briefly, in the long GnRH agonist protocol, Triptorelin (Diphereline, Ipsen Pharma, France) was administered in the mid-luteal phase of the preceding cycle, followed by ovarian

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stimulation with recombinant FSH (Gonal-F, Serono, Switzerland) from cycle day 2 or 3, based on patient age, BMI, and ovarian reserve. In the short GnRH antagonist protocol, ovarian stimulation commenced with rFSH and Cetrorelix (Cetrotide, Merck Serono, Germany) added when the leading follicle reached 14 mm, continuing until human chorionic gonadotropin (hCG) administration. Ovarian response was monitored through serial transvaginal ultrasound and serum estradiol measurements. When at least two follicles reached ≥ 18 mm, human chorionic gonadotropin (Pregnyl, Organon, Netherlands) was administered, with oocyte retrieval performed 34–36 hours later. Retrieved oocytes were classified as mature (MII) or immature (MI) based on their developmental stage.

Insemination methods included in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or a combined approach. Fertilization was assessed 16–20 hours post-insemination based on the presence of two pronuclei. Embryo quality was evaluated according to the Istanbul Consensus of Clinical Embryologists [8]. All assessments were conducted jointly by the embryology team. Embryo transfer was performed on day 2 or 3 post-oocyte retrieval, with a maximum of three embryos, depending on the patient's age, medical history, embryo quality and patients wish. Luteal phase support with intramuscular progesterone initiated from the day of oocyte retrieval. Pregnancy was confirmed by a positive serum β-hCG result 14 days post-transfer. Clinical pregnancy was verified via transvaginal ultrasound at six weeks of gestation.

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Statistical Analysis

Data were analyzed using appropriate statistical tests based on the nature of the examined variables. Categorical variables were assessed using the chi-square test (χ^2 test) to examine the distribution of infertility causes and stimulation protocols. Continuous variables were compared between groups using either the independent t-test or the Mann-Whitney U test, depending on the normality of data distribution. To evaluate the association between various predictors and IVF/ICSI success, univariate logistic regression analysis was performed. Variables with a significant association in the univariate analysis were subsequently included in a multivariate logistic regression model to identify independent predictors of a positive outcome. Statistical significance was set at $p < 0.05$. Results were reported as means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables, and as frequencies with percentages for categorical variables. Odds ratios (OR) with 95% confidence intervals (CI) were presented for logistic regression analyses. All statistical analyses were conducted using SPSS software (version 22.0, SPSS Inc., Chicago, IL).

Ethics: All patients were entirely informed about the research and all signed the informed consents for inclusion in the study in accordance with institutional ethical standards. The investigation approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade, Belgrade, Serbia (Number 29/XI-1).

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RESULTS

This study included 164 patients who underwent IVF/ICSI treatment. The mean patient age was 34.66 ± 3.69 years, with a mean BMI of 22.23 ± 2.65 kg/m². The mean duration of infertility was 4.86 ± 2.61 years (range: 1–17 years) (Table 1). The mean follicle-stimulating hormone (FSH) level was 7.24 ± 2.47 mIU/mL, while the mean luteinizing hormone (LH) level was 5.15 ± 2.66 mIU/mL. The mean estradiol (E2) concentration was 43.78 ± 19.45 pg/mL, and the mean progesterone (P4) concentration was 2.64 ± 1.75 ng/mL. The mean anti-Müllerian hormone (AMH) level was 2.55 ± 2.59 ng/mL. The total gonadotropin dose administered was 2205.03 ± 538.93 IU. The results are presented in table 2. The short stimulation protocol was significantly more prevalent than the long protocol (89.0% vs. 11.0%, $p < 0.0001$). The

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distribution of insemination techniques showed no significant difference, with IVF (42.1%), ICSI (29.3%), and a combined approach (28.7%) ($p = 0.06$) (Table 3). The most common cause of infertility was unexplained infertility (30.5%), followed by male factor (28.0%), tubal factor (18.9%), ovarian factor (18.3%), and combined infertility (4.3%). Most patients (65.2%) had 4–15 retrieved oocytes, while 19.5% had ≤3 oocytes, and 15.2% had >15 oocytes. Embryo grading showed that 56.7% of embryos were A-quality, 61.0% were B-quality, 17.1% were AB-quality, and 20.1% were C-quality, shown in Table 4. Among 164 treatment cycles, 88 cycles (53.7%) resulted in pregnancy, while 76 cycles (46.3%) did not lead to conception. Of the pregnancies, 71 (43.3%) progressed to live birth, 12 (7.3%) were biochemical pregnancies, and 5 (3.0%) resulted in miscarriage (Table 5).

Univariate logistic regression analysis identified BMI ≤ 25 kg/m² ($OR = 2.5$, $p < 0.05$), infertility duration ($OR = 1.9$, $p < 0.05$), number of mature oocytes ($p = 0.043$), and A-quality embryos ($OR = 1.87$, $p = 0.048$) as significant predictors of a positive outcome. The following factors that were identified are presented in table 6. Multivariate logistic regression confirmed that the number of mature oocytes ($p = 0.014$) and A-quality embryos ($p = 0.004$) were independent predictors of a successful pregnancy outcome. The results are presented in Table 7.

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DISCUSSION

This study highlights the pivotal factors that influence the success of ART procedures, emphasizing the importance of oocyte quantity and quality, embryo morphology, and hormonal balance in optimizing reproductive outcomes. Our results signify that a higher number of mature oocytes and A-quality embryos are independent predictors of a positive pregnancy outcome. Further, patients with a BMI lower than 25 kg/m² and a longer duration of infertility

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(> 3.5 years) had better treatment results, suggesting that healthy BMI optimizing hormonal balance, egg quality and overall treatment response, and reproductive history play a significant role in ART success.

In multivariate analysis, BMI stayed as a borderline significant factor that may have an impact, but it was not an independent predictor of success when the other factors were taken into account. The data from available literature is controversial. Some systematic reviews and meta-analyses have shown that women with a BMI over 25 have lower clinical pregnancy and live birth rates, as well as a higher risk of miscarriage compared to women with a BMI below 25 [9, 10], while others reported that BMI is not associated with the outcomes of fresh embryo transfer in women undergoing their first IVF/ICSI treatment [11].

Longer history of infertility is usually related to reduced chance of IVF/ICSI success, possibly due to the progression of underlying reproductive disorders over time [12]. Also, some studies have not found correlation between the duration of infertility and IVF/ICSI outcomes, indicating that other factors, such as maternal age and embryo quality, may have a greater impact on treatment success [13, 14]. Our study showed that a longer duration of infertility (> 3.5 years) was positively associated with IVF/ICSI success in univariate analysis, which is an uncommon finding, and could be explained with couples with longer infertility durations may have undergone more extensive diagnostic workups and previous treatments, and by the time they reached IVF, the underlying issues were better managed. Also, patients with long term infertility might be more motivated, and finally this was the group of patients that were less than 40 years old and that might have influenced o results. Still, in multivariate analysis, infertility duration was not retained as an independent predictor of success.

Results did not show correlation between baseline levels of FSH, LH, E2, AMH, dose of GT and pregnancy rates, what is in accordance with researches suggesting that elevated levels of

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FSH (>10 mIU/mL) may weaken ovarian response but do not necessarily correlate with lower clinical pregnancy rates. Elevated baseline estradiol (>60 pg/mL) is correlate with weaken ovarian response and lower pregnancy rates, as well and often mask the real level of FSH presenting ovarian reserve better than it actually is [1517]. A systematic review and meta-analysis examining progesterone levels at different phases of ART concluded that elevated baseline progesterone (> 1.5 ng/mL on day 2–3 of stimulation) does not significantly impact live birth or clinical pregnancy rates in fresh IVF cycles [18]. In our study univariate logistic regression analysis showed that respondents with lower levels of baseline progesterone had higher chance to achieve pregnancy.

Anti-Müllerian hormone beside as indicator of ovarian reserve is also a predictor of response to controlled ovarian stimulation. Our results did not show significant association among AMH levels and pregnancy rates, which is in accordance with other studies that suggest that higher AMH is correlate with a greater number of archived oocytes, but not necessarily with higher live birth rates [19]. Further, findings emphasized that very low AMH levels (<0.5 ng/mL) usually indicate weak ovarian response with low pregnancy chances. It's role as an independent predictor of IVF success has not been fully established [,20,21].

The number of oocytes retrieved during an ART cycle is labeled with an positive correlation with successful outcomes. Studies reported that retrieving among 6 to 15 oocytes yields the greatest potential for favorable results, then less, maintaining quality of embryos and decreasing the risk of ovarian hyper stimulation syndrome [22], but emphasizing that oocyte quality is more critical for the success of the procedure than the absolute number of retrieved oocytes. The high-quality oocytes are directly correlate with highest fertilization rate, embryo development, implantation rates and live births rate [23].

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In summary, our study underscores the significance of individualized evaluation in ART, with particular attention to the quantity and quality of oocytes and embryos, as well as patient-specific characteristics such as BMI and infertility history. The most consistent predictors of a successful outcome were a higher number of mature oocytes and top-quality embryos, reaffirming the central role of gamete and embryo competence in ART success. While BMI and duration of infertility showed associations in univariate analysis, they did not retain independent predictive value in multivariate models, highlighting the complexity and interplay of contributing factors. Baseline hormonal markers, including AMH and FSH, were not reliable indicators of pregnancy success, supporting the notion that their value lies more in assessing ovarian response than in predicting outcomes. The major limitations of our study, which decrease the strength of our findings, are its retrospective design and the limited sample size.

CONCLUSION

These findings advocate for a multifactorial and individualized approach to patient assessment and treatment planning in ART, rather than relying solely on traditional baseline parameters. In the realm of ongoing innovation and advancement in the area of assisted reproductive technologies a more precise and comprehensive understanding of the significance and contribution of predictive factors is crucial for optimizing outcomes. Additionally, development of predictive models using patient-specific factors could contribute to increase of ART success and live birth rates.

Conflicts of interest: None declared.

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Table 1. Distribution of demographic characteristics

Parameters		Total	%
Age	Up to 29	19	11.6%
	30–35	73	44.5%
	36+	72	43.9%
Smoking	No	131	79.9%
	Yes	33	20.1%
BMI	Up to 25	140	85.4%
	Over 25	24	14.6%

BMI – body mass index

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Table 2. Average values of demographic characteristics, baseline hormonal status, and gonadotropin (GT) dose

Parameters		**Number**	**Mean**	**SD**	**95% CI**		**Min.**	**Max.**
					Lower	Upper		
Age	Total	164	34.66	3.69	34.10	35.23	21	41
BMI	Total	164	22.23	2.65	21.82	22.64	18	29.40
Duration of infertility	Total	164	4.86	2.61	4.45	5.26	1	17
FSH	Total	160	7.24	2.47	6.86	7.63	2.60	15
LH	Total	156	5.15	2.66	4.73	5.57	0.40	25.20
E2	Total	157	43.78	19.45	40.71	46.85	10	100
AMH	Total	150	2.55	2.59	2.13	2.97	0.10	14.30
GT dosage	Total	159	2205.03	538.93	2120.62	2289.45	900.0	4125.0
P4	Total	164	2.64	1.75	2.37	2.91	0.22	9.31

BMI – body mass index; FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; AMH – anti-Müllerian hormone; P4 – progesterone

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Tabel 3. Stimulation protocol and insemination technique

		Total	%	χ^2 (df)	p-value
Stimulation protocol	GnRH agonists	18	11%	99.1 (1)	< 0.0001
	GnRH antagonists	146	89%		
Insemination technique	IVF	69	42.1%	5.65 (2)	0.06
	ICSI	48	29.3%		
	Combined	47	28.7%		
Total		164	100%		

IVF – in vitro fertilization; ICSI – intracytoplasmic sperm injection

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Table 4. Infertility cause disturbance, the number of retrieved oocytes and characteristics of embryos

				Total	%
Infertility cause		Male		46	28%
		Female	Tubal	31	18.9%
			Ovarian	30	18.3%
		Combined		7	4.3%
		Unknown		50	30.5%
The number of retrieved oocytes		< 3		32	19.5%
		4–15		107	65.2%
		> 15		25	15.2%
Quality of embryos	A quality embryo	No		71	43.3%
		Yes		93	56.7%
	B quality embryo	No		64	39%
		Yes		100	61%
	AB quality embryo	No		136	82.9%
		Yes		28	17.1%
	C quality embryo	No		131	79.9%
		Yes		33	20.1%

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Table 5. Assisted reproductive technologies outcomes

		Total	%
Outcomes	No pregnancy	76	46.3%
	Pregnancy	88	53.7%
Outcome of pregnancy	Delivery	71	43.3%
	Biochemical pregnancy	12	7.3%
	Miscarriage	5	3%

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Table 6. Univariate logistic regression analysis – predictive association with outcome

Parameters	B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Age	-0.05	0.04	1.17	1	0.280	0.95	0.88	1.04
BMI	-0.09	0.06	2.09	1	0.148	0.92	0.82	1.03
BMI – up to 25, over 25	-0.77	0.45	2.86	1	**0.091**	0.46	0.19	1.13
Smoking	0.04	0.39	0.01	1	0.909	1.05	0.49	2.25
Baseline concentrations of reproductive hormones								
FSH	0.00	0.06	0.00	1	0.995	1.00	0.88	1.13
LH	0.08	0.07	1.40	1	0.237	1.09	0.95	1.24
E2	0.01	0.01	0.90	1	0.344	1.01	0.99	1.02
AMH	0.03	0.06	0.28	1	0.596	1.03	0.91	1.17
GT dosage	0.00	0.00	0.16	1	0.686	1.00	1.00	1.00
P4	-0.28	0.10	8.10	1	**0.004**	0.75	0.62	0.92
Infertility								
Duration of infertility	0.08	0.06	1.51	1	0.219	1.08	0.96	1.22
Infertility cause	-0.04	0.10	0.17	1	0.681	0.96	0.78	1.17
Stimulation protocol	0.61	0.53	1.35	1	0.246	1.84	0.66	5.17
Technique	-0.22	0.19	1.36	1	0.244	0.80	0.55	1.16
Number of oocytes, fertilization rate and quality of embryos								
The number of oocytes	0.04	0.03	2.78	1	**0.096**	1.04	0.99	1.10
Up to 3,4–15, over 15	0.12	0.27	0.22	1	0.640	1.13	0.67	1.91
The number of mature oocytes	0.06	0.03	4.09	1	**0.043**	1.07	1.00	1.13
The number of fertilized oocytes	0.07	0.04	3.25	1	0.062	1.08	0.99	1.16
Fertilization rate	0.00	0.01	0.16	1	0.690	1.00	0.99	1.01
Quality of embryos	-0.51	0.19	7.36	1	**0.007**	0.60	0.42	0.87
A quality embryo	0.51	0.32	2.58	1	**0.048**	1.87	0.89	3.11

BMI – body mass index; FSH – follicle-stimulating hormone; LH – luteinizing hormone; E2 – estradiol; AMH – anti-Müllerian hormone; GT – gonadotropin; P4 – progesterone; B – unstandardized regression coefficient; S.E. – standard error; Wald – Wald statistic; Df – degrees of freedom; Sig. – statistical significance; Exp(B) – odds ratio

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Table 7. Multivariate logistic regression analysis: predictive association with the outcome

Parameters		**B**	**S.E.**	**Wald**	**Df**	**Sig.**	**Exp(B)**	**95% C.I. for Exp(B)**	
								Lower	Upper
Step first	BMI	-0.99	0.50	3.85	1	**0.050**	0.37	0.14	1.00
	Duration of infertility	0.59	0.37	2.58	1	0.108	1.80	0.88	3.69
	The number of oocytes	-0.10	0.10	1.09	1	0.297	0.90	0.75	1.09
	The number of mature oocytes	0.23	0.14	2.90	1	0.088	1.26	0.97	1.64
	The number of fertilized oocytes	-0.03	0.07	0.20	1	0.655	0.97	0.84	1.11
	Quality of embryos	-0.59	0.21	7.66	1	**0.006**	0.56	0.37	0.84
	Constant	3.12	1.15	7.36	1	0.007	22.61		
Step last	BMI	-0.88	0.49	3.25	1	0.072	0.41	0.16	1.08
	The number of mature oocytes	0.10	0.04	6.02	1	**0.014**	1.11	1.02	1.20
	Quality of embryos	-0.60	0.21	8.43	1	**0.004**	0.55	0.37	0.82
	Constant	3.80	1.00	14.57	1	0.000	44.66		

BMI – body mass index; B – unstandardized regression coefficient; S.E. – standard error; Wald – Wald statistic; Df – degrees of freedom; Sig. – statistical significance; Exp(B) – odds ratio

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