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Multivariate analysis of Lithuanian infertile women's biological factors

SUMMARY OF DOCTORAL DISSERTATION

Biomedical sciences,
Medicine 06B

VILNIUS 2018

The dissertation was prepared in 2012–2017 at the Clinic of Obstetrics and Gynecology, Faculty of Medicine, Vilnius University.

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VILNIAUS UNIVERSITETAS

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AMŠIEJIENĖ

Lietuvos nevaisingų moterų populiacijos biologinių veiksnių daugiamatė analizė

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ABBREVIATIONS

NICE - National Institute for Health and Care Excellence

IUI - intrauterine insemination

IVF - in vitro fertilization

ICSI - intracytoplasmic sperm injection

IMSI - intracytoplasmic morphologically selected sperm injection

ESHRE – European Society of Human Reproduction and Embryology

ASRM - American Society of Reproductive medicine

WHO – World Health organization

BMI – body mass index

WHR – waist to hip ratio

AMH – Anti-Müllerian hormone

AFC – antral follicle count

FSH – follicle-stimulating hormone

LH – luteinizing hormone

FAI – free androgen index

ART – assisted reproductive technologies

TFR – total fertility rate

INTRODUCTION

Infertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild, Adamson et al. 2009). Most (about 80-90 percent) couples get pregnant during the first year of planning and from 5 to 15 percent get pregnant during the second year (Kuohung 2015). One out of six couples experience fertility problems at least once during their fertile life (2016). About 186 millions of people have fertility problems (Inhorn and Patrizio 2015). Infertility is a chronic disease generating disability, affecting both physical and mental health (Schmidt, Christensen et al. 2005). According to WHO, infertility in women was ranked the 5th highest serious global disability (2011).

Family infertility can be analyzed through social, medical and demographical aspects. One of the most commonly used indicators is total fertility rate, which defines the total number of children born or likely to be born to a woman in her childbearing (reproductive) years if she were subject to the prevailing rate of age-specific fertility in the population. This rate should be more than 2,1 to sustain population levels. The term "lowest-low fertility" is defined as TFR at or below 1.3. In the European Union TFR is about 1,58 (2017). In modern societies there is a trend for families to have fewer children and for women to delay childbearing (Stankūnienė, Baublytė et al. 2016, Stankūnienė 2017). Fertility decreases with increasing age, so delaying childbearing means bigger need for medical help such as ART (Baird, Collins et al. 2005, 2009, Daniluk and Koert 2012). Advanced maternal age is associated with lower fertility and various comorbidities, but most women rely on modern medical technologies and think that with ART women can get pregnant until menopause (Daniluk, Koert et al. 2012). The ability to bear children is just one of many factors influencing fertility. Sexual behavior, family size limitation, social situation, advanced maternal age, usage of contraceptive methods, ART possibilities and other factors can be influencing women’s reproductive health (Bonde and Olsen 2008).

In Lithuania TFR started declining steadily after 1990, reaching as low as 1,23 in 2002. From 2006 it started going up slowly, but is still low – 1,69 in 2016 (Stankūnienė, Jasilionis et al. 2014). Natural increase rate is negative for many years. From 1992 to 2018, Lithuania's population decreased by 23% from 3.7 million to 2.81 million (Drąsutienė 2007, Stankūnienė 2017). Maternal age increased significantly in Lithuania: in 2001, the average age was 27, and in 2016, - 29.1 years (Medical data of Birth Register from 2000 through 2016). The same trend is seen all over the Europe (Ledger 2009, Beaujouan and Sobotka 2017).

Lithuania’s demographical situation and family infertility problems can partially be solved using modern medical technologies such as ART. However, it is not always clear what factors influence the success of ART. This study can reveal part of factors influencing infertility in Lithuanian society.

1. AIM OF DISSERTATION

To evaluate age, anthropometrical measures and ovarian reserve of Lithuanian infertile women and to perform multivariate analysis of factors influencing success of ART.

2. OBJECTIVES OF THE DISSERTATION

1. To evaluate the influence of woman’s age on pregnancy, live birth and miscarriage rates after ART.
2. To evaluate the association of body size and composition with pregnancy, live birth and miscarriage rates after ART.
3. To evaluate the influence of ovarian reserve on pregnancy, live birth and miscarriage rates after ART.

4. To evaluate the differences of analyzed factors in different women and men infertility groups.
5. To perform multivariate analysis of all analyzed factors.

3. RELEVANCE AND SCIENTIFIC NOVELTY OF THE RESEARCH

This research is one of few scientific studies in Lithuania that analyses causes of infertility and biological factors influencing ART success. The demographic situation in our country has reached a critical point. Decreasing birth rates raise concern for society and in particular for the medical community. The search for a link between the morphological characteristics of the woman's health and her physical condition is the subject of research in many countries. Various factors affecting pregnancy and delivery after ART are discussed in scholarly literature. The links between bodies' morphological and biochemical markers and their relationship with female health are being studied by Vilnius University anthropologists and clinicians in the last decades. The specifics of each country's life, social factors are associated with public health. Changing conditions of living, specific diet, ethnical and climatic factors affect these relationships. Therefore, it is no coincidence that the topic of scientific work done at the Vilnius University Clinic of Obstetrics and Gynecology is intended to explain the associations mentioned above. This research, aiming to identify infertile women's anthropometric and biochemical markers, extends the research of Vilnius University scientists on the links between female anthropometric and metabolic indexes and complements the research of other countries.

The findings of this research can be useful for doctors consulting infertile families, predicting probability of pregnancy and delivery after ART and choosing the best examination and treatment plan.

4. MATERIALS AND METHODS

Patients undergoing IVF in Vaisingumo klinika between 2013 and 2015 were included in this research.

General anthropometric and metabolic biochemical (hormone) indicators were obtained. The study used standard anthropometric methods. The following body size anthropometric indicators were measured: height, body weight, waist circumference, hip circumference. The circumferences of the body (cm) in women were measured in standing position: the waist circumference (in the middle between the lower rib cage and the pelvic crests) and the hip circumference (measuring the widest site of gluteal region). Digit length was measured on the palmar surface of the hand from the basal crease of the digit to the tip using Vernier calipers.

Hormones (FSH, LH, estradiol, testosterone, SHBG, AMH) were measured on cycle day 3-5 using Roche Cobas e411 analyzer. AFC was measured on cycle day 2-3 using transvaginal ultrasound.

Daily gonadotrophin dose was started on cycle day 2-3. When dominant follicle reached a maximum diameter of 14 mm, daily GnRh antagonist injections were given. When at least 3 follicles reached 18 mm in diameter, human chorionic gonadotropin was administered. Transvaginal oocyte retrieval was performed 36 hours after hCG injection. Oocytes were fertilized conventionally or via ICSI. Embryo transfer was performed using Cook catheter on day 2-3. Surplus embryos were cultured to the blastocyst stage. Cryopreservation was performed for surplus embryos. Only clinical pregnancies were evaluated. A single serum β-hCG measurement was performed 12 days after embryo transfer procedure. If serum hCG was >40 IU/l, indicating pregnancy, the luteal support (Crinone 8 % one applicator per day vaginally until the 8th week of gestation) was continued until the ultrasound scans. Clinical pregnancy was confirmed when an intrauterine gestational sac with fetal heartbeat was detected during transvaginal ultrasound examination.

Women were divided to 3 age groups:

- 35 years old and younger
- 36-40 years old
- Older than 40 years

Women were divided to 4 groups according to BMI:

- < 18,5 - underweight
- 18,5 - 24,9 - normal range
- 25 - 29,9 - overweight
- ≥ 30 - obese

Women were divided to 4 groups according to waist to hip ratio (Kidy FF, Dhalwani N et al. 2017):

- < 0,75 - excellent
- 0,75 - 0,79 - good
- 0,80 - 0,86 – average
- > 0,86 – at risk

Women were divided to 3 groups according to AFC:

- ≤ 4 – likely low ovarian response to stimulation
- 5-16 – likely normal ovarian response to stimulation
- >16 – likely high ovarian response to stimulation

Women were divided to 3 groups according to AMH:

- ≤ 0,76 ng/ml - likely low ovarian response to stimulation
- 0,77-3,49 ng/ml - likely normal ovarian response to stimulation
- ≥ 3,5 ng/ml - likely high ovarian response to stimulation

Women were divided to 3 groups according to FSH:

- FSH > 8,9 IU/L- likely low ovarian response to stimulation
- FSH 4–8,9 IU/L - likely normal ovarian response to stimulation

- FSH < 4,0 IU/L - likely high ovarian response to stimulation

The statistical analysis of the data was performed using “IBM SPSS”. The calculation of anthropometric and biochemical indicators mean values, standard deviations, minimum and maximum values was performed. The data of different groups were compared using Student’s t test, chi-square and ANOVA analysis. Logistic regression and multivariate factor analysis were performed. The selected level of statistical significance – $p<0.05$.

5. RESULTS

5.1. Physical status of participants

5.1.1. Characteristics of women

863 women aged from 21 to 47 (M = 33,4, SN = 4,48) participated in this research. 1166 controlled ovarian hyperstimulation cycles and oocyte retrievals were performed. Women with female factor infertility were statistically significantly (p=0,007) older (N=749, M=33,67, SN=4,33) than women with male factor infertility (N=417, M=32,93, SN=4,71). Embryo transfer was performed in 1051 case (90,14 %). Embryo transfer was not performed in 115 cases (table 1).

Table 1. Reasons for canceled embryo transfer

Reasons	**N**	**%**
No oocytes retrieved	18	15,65
No spermatozoon retrieved	2	1,74
No embryos formed	55	47,83
No good quality embryos formed	14	12,17
Freeze all	26	22,61
Total	115	100

On average 9,46 oocytes were retrieved (SD=6,11, min-max 0-45 oocytes) and 5,08 embryos were formed (SD=3,84, min-max 0-29 embryos) during one cycle. Statistically significantly (p=0,000) less oocytes were retrieved for women with female factor infertility (N=749, M=8,87, SD=6) compared to women with male factor infertility (N=416, M=10,52, SD=6,17). The mean embryo number did not differ significantly (N=748, M=5,03, SD=3,88 vs N=416, M=5,17, SD=3,77). Pregnancy rate per oocyte retrieval was 40,1 %, live birth rate - 25,6 % (N=298). Multiple pregnancy rate - 17,2 % (N=79). Pregnancy rate per transfer - 44,4 % (N=467), live birth rate - 28,4 % (N=298). Pregnancy and live birth rate did not differ in women with female factor infertility compared to women with male factor infertility.

Indications for ART are listed in table 2.

Table 2. Indications for ART

Indications	**N**	**%**
Tubal infertility	280	24
Endometriosis	155	13,3
Ovulatory dysfunction	47	4
Male factor	417	35,8
Unexplained infertility	247	21,2
Other reasons	20	1,7
Total	1166	100

Table 3. Pregnancy and delivery rates

Indications	Pregnancy		No pregnancy		Delivery	
	N	**%**	**N**	**%**	**N**	**%**
Tubal infertility	109	41,4	154	58,6	69	26,2
Endometriosis	66	48,9	69	51,1	52	38,5
Ovulatory dysfunction	14	35,9	25	64,1	8	20,5
Male factor	169	45,2	205	54,8	103	27,5
Unexplained infertility	104	46,6	119	53,4	62	27,8
Other reasons	5	29,4	12	70,6	4	23,5
Total	467	44,4	584	55,6	298	28,4

Pregnancy and delivery rates presented in table 3 were not significantly different in various indication groups (p=0,384 and p=0,110).

5.1.2. Women's body size

Table 4. Women's anthropometrical indicators

Measure	**N**	**Min**	**Max**	**M**	**SD**
Height (m)	1166	1,48	1,89	1,69	0,05
Weight (kg)	1166	43	130	66,18	11,69
BMI	1166	16,05	44,98	23,19	3,96
Waist circumference (cm)	640	54	125	76,38	12,31
Hip circumference (cm)	638	68	138	96,06	10,78
WHR	638	0,62	1,34	0,79	0,08

Table 4 shows women's anthropometrical indicators. Mean BMI is within normal range (18,5-24,99). Waist to hip ratio is associated with woman's reproductive health (ability to get pregnant and deliver). Mean waist to hip ratio was 0,79.

Table 5. Women's anthropometrical indicators in various indication groups

Indicator	Cause of infertility						
	Female factor			Male factor			
	N	M	SD	N	M	SD	P
Height (m)	749	1,69	0,05	417	1,69	0,05	0,044
Weight (kg)	749	65,84	11,72	417	66,8	11,64	0,180
BMI	749	23,15	4,07	417	23,27	3,75	0,616
Waist circumference (cm)	410	76,49	12,64	230	76,2	11,72	0,772
Hip circumference (cm)	409	95,69	10,77	229	96,7	10,78	0,257
WHR	409	0,8	0,09	229	0,79	0,07	0,072

Anthropometrical indicators were similar in women with female factor infertility compared to women with male factor infertility (table 5).

Table 6. Digit length

Indicator	**N**	**Min**	**Max**	**M**	**SD**
II digit (cm)	648	5,5	9	6,67	0,33
IV digit (cm)	648	5	10	6,75	0,39
2D:4D ratio	648	0,7	1,12	0,99	0,27

We measured the length of 2nd and 4th digit of 648 women. 2D:4D ratio is sexually dimorphic and shows the exposure to androgens and estrogens in prenatal period. Mean 2D:4D ratio was 0,99 (table 6).

Table 7. Digit length in various indication groups

Indicator	**Cause of infertility**						
	Female factor			**Male factor**			
	N	**M**	**SD**	**N**	**M**	**SD**	**P**
II digit (cm)	412	6,67	0,32	236	6,68	0,35	0,543
IV digit (cm)	412	6,73	0,36	236	6,79	0,42	**0,036**
2D:4D ratio	412	0,99	0,03	236	0,98	0,03	**0,001**

Mean 2D:4D ratio was statistically significantly higher in women with female factor infertility compared to women with male factor infertility (table 7).

5.1.3. Biochemical markers

Table 8 shows biochemical markers that are important in infertility treatment. AMH plays an important role in predicting response to ovarian stimulation. Mean AMH level was within normal range (M=3.54 μg/L).

Table 8. Biochemical markers

Indicator	**N**	**Min**	**Max**	**M**	**SD**
FSH (mIU/ml)	577	1,93	17,4	7,28	2,23
LH (mIU/ml)	577	1,1	21	6,15	2,75
Testosterone (nmol/l)	366	0,08	34,4	1,75	3,91
SHBG (nmol/l)	346	19,77	200	85,15	37,93
FAI	337	0,1	10,95	1,51	1,28
AMH (μg/L)	325	0,03	18,92	3,54	3,17

Mean AMH was statistically significantly higher in women with male factor infertility compared to women with female factor infertility (table 9).

Table 9. Biochemical markers in various indication groups

Indicator	Cause of infertility						
	Female factor			Male factor			
	N	M	SD	N	M	SD	P
FSH (mIU/ml)	375	7,36	2,24	202	7,13	2,2	0,233
LH (mIU/ml)	358	6,1	2,63	199	6,24	2,95	0,563
Estrodial (pmol/l)	237	273,47	859,98	143	222,26	371,35	0,500
Testosterone (nmol/l)	237	1,55	3,55	129	2,11	4,51	0,198
SHBG (nmol/l)	226	85,68	38	118	84,12	37,94	0,718
FAI	221	1,5	1,31	116	1,52	1,22	0,912
AMH (µg/L)	214	3,23	3,15	111	4,14	3,14	**0,014**

5.1.4. Ultrasound testing of ovarian reserve

Female genitalia, ovarian reserve and ovarian response to gonadotropin stimulation can be evaluated by ultrasound testing. We measured antral follicle count of 325 women. Mean AFC was 11,91 (min-max 4-33). Mean AFC was statistically significantly (p=0,024) higher in women with male factor infertility (N=111, M=12,94, SD=5,67) compared to women with female factor infertility (N=214, M=11,38, SN=5,99).

5.2. Differences between women who conceived and who did not

Women who conceived were statistically significantly (p=0,000) younger (M=32,72 years, SD=4,08, min-max 21-47 years) than those who did not conceive (M=33,8 years, SD=4,68, min-max 22-47 years) after ART.

Women who got pregnant after ART were statistically significantly taller, leaner and had lower BMI and WHR than women who did not conceive (table 10).

Table 10. Anthropometrical indicators

Indicator	Pregnancy			No pregnancy			P
	N	M	SD	N	M	SD	
Height (m)	467	1,7	0,05	584	1,68	0,52	**0,002**
Weight (kg)	467	64,09	9,71	584	67,48	12,63	**0,000**
BMI	467	22,31	3,25	584	23,76	4,24	**0,000**
Waist circumference (cm)	254	75,33	11,05	327	77,47	13,24	**0,034**
Hip circumference (cm)	252	95,67	10,26	327	96,67	11,28	0,268
WHR	252	0,79	0,07	327	0,8	0,09	**0,033**

Mean 2D:4D ratio was not different in women who got pregnant after ART compared to those who did not get pregnant. Mean AMH was statistically significantly higher in women with male factor infertility compared to women with female factor infertility (table 11).

Table 11. Digit length

Indicator	Pregnancy			No pregnancy			P
	N	M	SD	N	M	SD	
II digit (cm)	255	6,69	0,37	332	6,67	0,3	0,546
IV digit (cm)	255	6,77	0,43	332	6,75	0,36	0,608
2D:4D ratio	255	0,99	0,03	332	0,99	0,03	0,979

Table 12. Biochemical markers

Indicator	Pregnancy			No pregnancy			P
	N	M	SD	N	M	SD	
FSH (mIU/ml)	239	7,07	2,07	286	7,36	2,22	0,115
LH (mIU/ml)	232	6,1	2,51	275	6,16	2,74	0,799
Testosterone (nmol/l)	161	1,87	4,64	176	1,7	3,44	0,692
SHBG (nmol/l)	151	87,83	37,4	168	83,9	38,65	0,358
FAI	148	1,33	0,92	162	1,66	1,54	**0,017**
AMH (µg/L)	130	3,72	3,11	165	3,58	3,05	0,684

Only FAI was statistically significantly higher in women who did not conceive compared to whose who did (table 12).

Mean AFC was statistically significantly (p=0,025) higher in women who got pregnant (N=130, M=13,05, SD=5,71) after ART compared to those who did not get pregnant (N=165, M=11,5, SD=5,61). Significantly (p=0,001) higher dose of gonadotropins was used for women who did not get pregnant (N=556, M=1563,4 IU, SD=560,96) after ART compared to those who got pregnant (N=452, M=1540,64 IU, SD=464,74). The retrieved number of oocytes was statistically significantly (p=0,007 higher in women who got pregnant (N=467, M=10,18 SD=5,69) after ART compared to those who did not get pregnant (N=584, M=9,05, SN=5,44). Statistically significantly (p=0,000) higher number of embryos formed in women who got pregnant (N=467, M=5,89, SD=3,59), after ART compared to those who did not get pregnant (N=584, M=4,88, SD=3,4).

5.3. Differences between women who gave birth and who miscarried

467 women got pregnant after ART, 298 (63,8 %) of them gave birth. Mean age of women who delivered after ART was 32,2 years: SD 3,7, min-max 21-47 years. Mean age of women who suffered a miscarriage after ART was 33,63 years: SD 4,54, min-max 23-44 years. The difference was statistically significant, p=0,000.

We found no significant differences between women who gave birth and miscarried after ART in terms of height and weight, but women who miscarried had significantly higher BMI compared with those who gave birth after ART (table 13).

Table 13. Body size differences between women who delivered and miscarried

Indicator	Delivery			Miscarriage			
	N	M	SD	N	M	SD	P
Height (m)	298	1,7	0,05	169	1,69	0,06	0,063
Weight (kg)	298	63,63	9,0	169	64,91	10,82	0,170
BMI	298	22,06	2,98	169	22,77	3,64	**0,025**
Waist circumference (cm)	159	74,4	10,09	95	76,89	12,4	0,081
Hip circumference(cm)	157	95,2	9,21	95	96,45	11,8	0,350
WHR	157	0,78	0,07	95	0,8	0,07	0,082

Table 14. 2D:4D ratio differences

Indicator	Delivery			Miscarriage			
	N	M	SD	N	M	SD	P
II digit (cm)	160	6,71	0,41	95	6,65	0,3	0,244
IV digit (cm)	160	6,79	0,5	95	6,74	0,3	0,395
2D:4D ratio	160	0,99	0,03	95	0,99	0,02	0,499

We found no differences in 2D:4D ratio between women who gave birth after ART and those who suffered a miscarriage after ART (table 14).

Table 15. Differences in biochemical markers

Indicator	Delivery			Miscarriage			
	N	M	SD	N	M	SD	P
FSH (mIU/ml)	159	7,08	2,02	80	7,04	2,19	0,909
LH (mIU/ml)	159	5,97	2,46	73	6,39	2,62	0,235
Testosterone (nmol/l)	106	1,94	4,97	55	1,74	3,97	0,792
SHBG (nmol/l)	102	88,19	35,81	49	87,06	40,89	0,863
FAI	99	1,29	0,92	49	1,40	0,94	0,478
AMH (µg/L)	87	3,98	3,34	43	3,21	2,53	0,187

We found no differences in biochemical markers between women who gave birth after ART and those who suffered a miscarriage after (table 15).

The mean number of oocytes retrieved was higher in women who suffered a miscarriage after ART compared to women who delivered, but the mean number of embryos formed was the same in both groups (table 16).

Table 16. Differences between women who delivered and miscarried

Indicator	Delivery			Miscarriage			
	N	**M**	**SD**	**N**	**M**	**SD**	**P**
AFC	87	13,06	5,48	43	13,02	6,24	0,975
Dose of gonadotropins (IU)	292	1418,73	452,87	160	1508,88	481,65	**0,048**
Number of oocytes retrieved	298	9,96	5,66	169	10,57	5,73	0,264
Number of embryos formed	298	5,93	3,65	169	5,82	3,49	0,757

Significantly higher dose of gonadotropins was used for ovarian stimulation in women who later miscarried after ART compared with women who delivered. The mean number of antral follicles was similar in both groups (table 16).

5.4. The influence of age on ART success

Female age is one of the most important factors influencing fertility. Increasing age, especially if woman is older than 35 years, is associated with decreasing fertility. Most of women (N=727, 69,2 %) who participated in this research were younger than 36 years (fig.1).

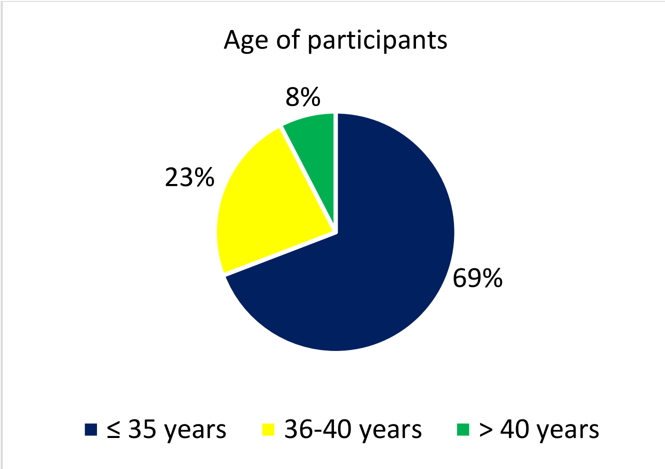

Fig. 1. Age of participants

The pregnancy rate was statistically significantly higher (p=0,000) in younger women, reaching 48,8 % (N=355) in women who were younger than 36 years. Delivery rates were also statistically significantly (p=0,000) different in different age groups (table 17).

Table 17. Pregnancy and delivery rates in different age groups

Female age	**Pregnancy**		**No pregnancy**		**Delivery**	
	N	**%**	**N**	**%**	**N**	**%**
≤ 35 years	355	48,8	372	51,2	245	33,7
36-40 years	96	39,3	148	60,7	51	20,9
>40 years	16	20	64	80	2	2,5
Total	467	44,4	584	55,6	298	28,4

Advanced maternal age is associated with higher risk of miscarriage. Miscarriage rate was statistically significantly (p=0,000) higher in older women, reaching 87,5 % in women older than 40 years (table 18).

Table 18. Delivery and miscarriage rates of women who got pregnant after ART

Female age	**Delivery**		**Miscarriage**	
	N	**%**	**N**	**%**
≤ 35 years	245	69	110	31
36-40 years	51	53,1	45	46,9
>40 years	2	12,5	14	87,5
Total	298	63,8	169	36,2

The odds of pregnancy after ART was 1,8 times higher in women younger than 36 years old compared with older women (OR- 1,8; 95% CI 1,4-2,4). The odds of delivery after ART was 2,6 times higher in women younger than 36 years old compared with older women (OR – 2,6; 95% CI 1,9-3,6). The odds of miscarriage after ART was 2,5 times higher in women older than 35 years old compared with younger women (OR 2,5; 95% CI 1,6-3,8).

5.5. The influence of obesity on ART success

Obesity has a negative impact on reproductive health. Obese women tend to have menstrual cycle and ovulatory dysfunctions and perinatal complications occur more often during pregnancy.

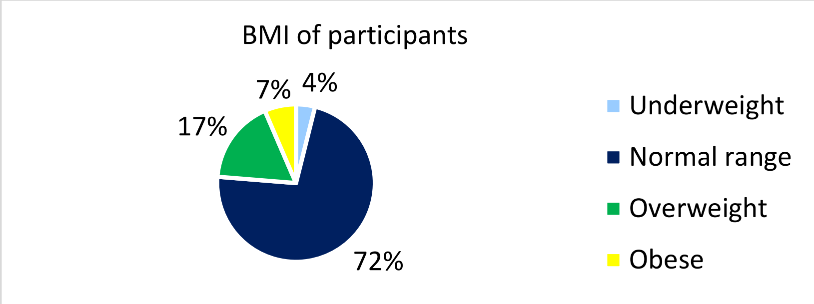

Fig. 2. BMI of participants

Fig. 2 shows the distribution of participants according to the BMI. Most of participants were in the normal BMI range (N=760, 72 %).

Table 19. Pregnancy and delivery rates in different BMI groups

BMI	Pregnancy		No pregnancy		Delivery	
	N	%	N	%	N	%
Underweight	20	48,8	21	51.2	13	31.7
Normal range	375	49.3	385	50.7	246	32.4
Overweight	31.5	31.5	124	68.5	30	16.6
Obese	14	20.6	54	79.4	8	11.8
Total	466	44.4	584	55.6	297	28.3

The biggest pregnancy rate was observed in normal BMI range group (N=375, 49,3 %). Pregnancy rate in obese women group was more than two times lower (N=14, 20,6 %). The difference was statistically significant (p=0,000). Delivery rates were also statistically significantly (p=0,000) different in different BMI groups. The biggest delivery rate was observed in normal BMI range group (N=246, 32,4 %) while delivery rate in obese women only reached 11,8 % (N=8) (table 19).

Table 20. Delivery and miscarriage rates of women who got pregnant after ART

BMI	Delivery		Miscarriage	
	N	**%**	**N**	**%**
Underweight	13	65	7	35
Normal range	246	65.6	129	34.4
Overweight	30	52.6	27	47.4
Obese	8	57.1	6	42.9
Total	297	63.7	169	36.3

The trend towards higher miscarriage rate in overweight and obese women was noticed, but the differences were not statistically significant (p=0.275) (table 20).

The odds of pregnancy after ART was 2,5 times higher in women who had no overweight (BMI <25) compared with obese women (OR-2,5; 95% CI 1,8-3,3). The odds of delivery after ART was 2,7 times higher in women who had no overweight (BMI <25) compared with obese women (OR – 2,7; 95% CI 1,8-3,9). The odds of miscarriage after ART was 1,7 times higher in obese women (BMI ≥25) compared with women who had no overweight (OR 1,7; 95% CI 1-2,8).

Table 21. Pregnancy rate in different BMI and age groups

BMI	**≤35 years**	**36-40 years**	**>40 years**	**P**
Underweight	48.3 %	44.4 %	66.7 %	0.797
Normal range	53.0 %	43.4 %	23.9 %	**0.000**
Overweight	33.0 %	36.1 %	10.0 %	0.083
Obese	25.7 %	18.2 %	9.1 %	0.465
P	**0.000**	0.135	0.086	

We noticed the trend that in all age groups the pregnancy rate was going down when women's BMI was higher (table 21).

Table 22. Delivery rates in different BMI and age groups

BMI	**≤35 years**	**36-40 years**	**>40 years**	**P**
Underweight	37.9 %	11.1 %	33.3 %	0.319
Normal range	37.2 %	24.3 %	0.0 %	**0.000**
Overweight	19.0 %	16.4 %	5.0 %	0.307
Obese	14.3 %	13.6 %	0.0 %	0.416
P	**0.000**	0.382	**0.003**	

The delivery rate was also going down when women's BMI was higher. Statistically significant difference was only observed in young (≤35 years) and older (>40 years) women's group (table 22).

Table 23. Miscarriage rate of women who got pregnant after ART

	≤35 years	**36-40 years**	**>40 years**	**P**
Underweight	21.4 %	75.0 %	50.0 %	0.126
Normal range	29.9 %	43.9 %	100.0 %	**0.000**
Overweight	42.4 %	54.6 %	50.0 %	0.676
Obese	44.4 %	25.0 %	100.0 %	0.394
P	0.315	0.426	0.077	

Table 23 shows the miscarriage rate of women who got pregnant after ART which was as high as 100 % in older women (>40 years) who were in the normal BMI age and obese. Miscarriage rate was statistically significantly influenced by age only in normal BMI range group.

5.6. The influence of WHR on ART success

WHR correlates with fertility. Circulating estrogen preferentially stores lipid deposits in the gluteofemoral region, including the buttocks and thighs. Body fat deposition can be evaluated by measuring waist to hip ratio. Fig. 3 shows the distribution of participants according to WHR. Most of participants (N=319, 55 %) had WHR lower than 0,8.

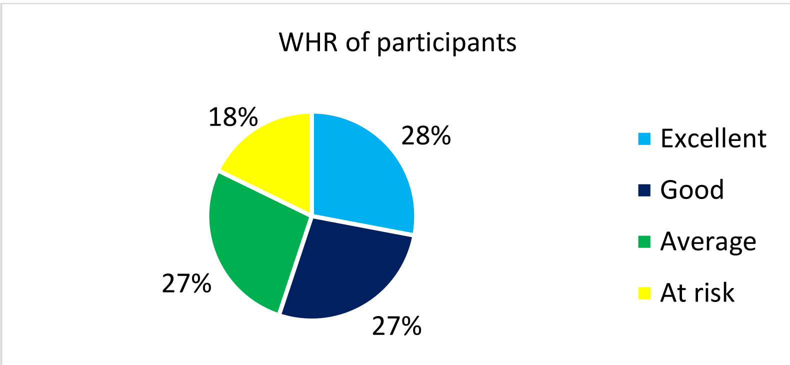

Fig. 3. Waist to hip ratio of participants

Table 24 shows pregnancy and delivery rates in different WHR groups. Lower pregnancy and delivery rates were observed in women who had high WHR, but the differences were not significant (p=0,185; p=0,068).

Table 24. Pregnancy and delivery rates in different WHR groups

WHR	Pregnancy		No pregnancy		Delivery	
	N	%	N	%	N	%
Excellent	76	46,9	86	53,1	48	29,6
Good	71	45,2	86	54,8	51	32,5
Average	70	44,6	87	55.4	39	24,8
At risk	35	34,0	68	66,0	19	18,4
Total	252	43,5	324	56,5	157	27,1

We noticed that the miscarriage rate is higher in women who have higher WHR, but the differences were not significant (p=0.170) (table 25).

Table 25. Delivery and miscarriage rates of women who got pregnant after ART

WHR	Delivery		Miscarriage	
	N	%	N	%
Excellent	48	62,3	28	36,8
Good	51	71,8	20	28,2
Average	39	55,7	31	44,3
At risk	19	54,3	16	45,7
Total	157	62,3	95	37,7

The odds of pregnancy after ART was 1,4 times higher in women who had WHR≤0,8 compared with women who had WHR>0,8 (OR-1,4; 95% CI 1-1,9). The odds of delivery after ART was 1,8 times higher in women who had WHR≤0,8 compared with women who had WHR>0,8 (OR – 1,8; 95% CI 1,2-2,7). The odds of miscarriage after ART was 1,9 times higher in women who had WHR>0,8 compared with women who had WHR≤0,8 (OR 1,9; 95% CI 1,1-3,3).

Table 26. Pregnancy rates in different WHR and age groups

WHR	**≤35 years**	**36-40 years**	**>40 years**	**P**
Excellent	51,3 %	31,4 %	50 %	0,116
Good	48,2 %	45,9 %	10 %	0,067
Average	53,3 %	30,8 %	9,1 %	**0,003**
At risk	35,9 %	35,5 %	12,5 %	0,409
P	0,146	0,498	0,091	

When female age and WHR is increasing, the pregnancy rate is decreasing, but statistically significant differences were only observed in average WHR group. The same tendencies are seen in delivery rates (tables 26 and 27).

Table 27. Delivery rates in different WHR and age groups

WHR	**≤35 years**	**36-40 years**	**>40 years**	**P**
Excellent	32,8 %	22,9 %	12,5 %	0,292
Good	37,3 %	24,3 %	10 %	0,101
Average	30,8 %	15,4 %	0 %	**0,023**
At risk	23,4 %	12,9 %	0 %	0,174
P	0,301	0,552	0,515	

We noticed the trend that when the age and WHR was increasing, miscarriage rate was increasing as well. However, the differences were not statistically significant (table 28).

Table 28. Miscarriage rate of women who got pregnant after ART

WHR	**≤35 years**	**36-40 years**	**>40 years**	**P**
Excellent	36,1 %	27,3 %	75 %	0,229
Good	22,6 %	47,1 %	0 %	0,123
Average	42,1 %	50,0 %	100 %	0,466
At risk	34,8 %	63,6 %	100 %	0,156
P	0,184	0,394	0,344	

5.7. The influence of ovarian reserve on ART success

Success of ART depends on the ovarian response to gonadotropin stimulation. Factors, influencing ovarian response, may have prognostic value in predicting pregnancy and delivery rates after ART. Antral follicle count shows ovarian reserve. Fig.4 shows distribution of participants according to AFC.

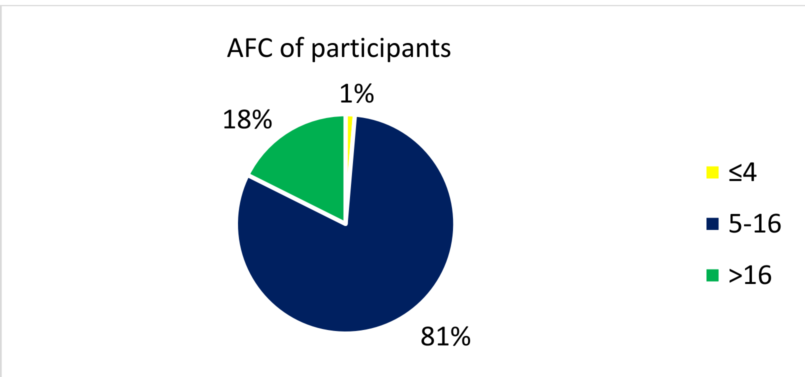

Fig. 4. AFC of participants

Table 29. Pregnancy and delivery rates in different AFC groups

AFC	Pregnancy		No pregnancy		Delivery	
	N	**%**	**N**	**%**	**N**	**%**
≤4	0	0	4	100	0	0
5-16	105	43,9	134	56,1	72	30,1
>16	25	48,1	27	51,9	15	28,8
Total	130	44,1	165	55,9	87	29,5

Table 29 shows pregnancy and delivery rates in different AFC groups. No woman got pregnant in the low AFC group (AFC ≤4), but we found no significant differences in pregnancy and delivery rates between different AFC groups (p=0,174; p=0,421).

Table 30. Delivery and miscarriage rates of women who got pregnant after ART

AFC	Delivery		Miscarriage	
	N	**%**	**N**	**%**
≤4	0	0	0	0
5-16	72	68,6	33	31,4
>16	15	60,0	10	40,0
Total	87	66,9	43	33,1

Delivery and miscarriage rates of women who got pregnant after ART were not significantly different in different AFC groups (p=0,413) (table 30).

Table 31. Pregnancy rates in different AFC and age groups

AFC	≤35 years	36-40 years	>40 years	P
≤4	-	-	0 %	-
5-16	53,8 %	34,7 %	12,5 %	**0,000**
>16	52,2 %	16,7 %	-	0,102
P	0,843	0,367	0,454	

Table 31 shows pregnancy rates in different AFC and age groups. We found statistically significant differences only in likely normal ovarian response group (AFC 5-16). When the age is increasing, the probability of pregnancy decreases even when ovarian reserve is normal. We see the same trend when analyzing delivery rates in different AFC and age groups (table 32). When ovarian reserve is normal, delivery rate (41,3%) in women younger than 36 years old is more than 2 times higher compared with older women (18,1 %).

Table 32. Delivery rates in different AFC and age groups

AFC	≤35 years	36-40 years	>40 years	P
≤4	-	-	0 %	-
5-16	41,3 %	18,1 %	0 %	**0,000**
>16	32,6 %	0 %	-	0,097
P	0,296	0,254	-	

Miscarriage rate of women who got pregnant after ART was significantly increasing with age in normal ovarian reserve group (Table 33).

Table 33. Miscarriage rate of women who got pregnant after ART

AFC	≤35 years	36-40 years	>40 years	P
≤4	-	-	-	-
5-16	23,4 %	48 %	100 %	**0,002**
>16	37,5 %	100 %	-	0,211
P	0,172	0,308	-	

Level of AMH shows ovarian reserve and likely ovarian response to gonadotropin stimulation. Fig. 5 shows distribution of research participants according to AMH level. AMH level was 0,77-3,49 ng/ml in 55 % (N=162) of participants, meaning that the likely ovarian response to stimulation was normal.

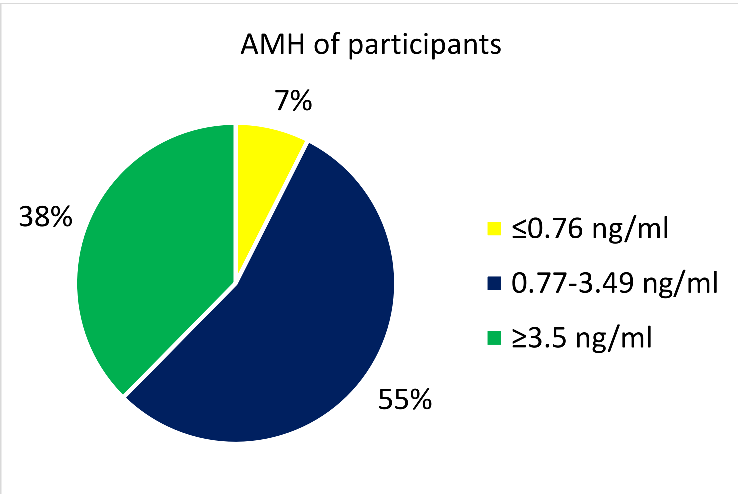

Fig 5. AMH of participants

Table 34. Pregnancy and delivery rates in different AMH groups

AMH	Pregnancy		No pregnancy		Delivery	
	N	%	N	%	N	%
≤0,76 ng/ml	9	40,9	13	59,1	5	22,7
0,77-3,49 ng/ml	72	44,4	90	55,6	46	28,4
≥3,5 ng/ml	49	44,1	62	55,9	36	32,4
Total	130	44,1	165	55,9	87	29,5

Pregnancy and delivery rates were similar in different AMH groups, no significant differences were found (p=0,952; p=0,595) (table 34).

Table 35. Delivery and miscarriage rates of women who got pregnant after ART

AMH	Delivery		Miscarriage	
	N	%	N	%
≤0,76 ng/ml	5	55,6	4	44,4
0,77-3,49 ng/ml	46	63,9	26	36,1
≥3,5 ng/ml	36	73,5	13	26,5
Total	87	66,9	43	33,1

We noticed the trend that when AMH is increasing, miscarriage rate is decreasing in women who got pregnant after ART, but there were no statistically significant differences (p=0,412) (table 35).

Table 36. Pregnancy rate in different AMH and age groups

AMH	≤35 years	36-40 years	>40 years	P
≤0,76 ng/ml	66,7 %	37,5 %	0 %	0,051
0,77-3,49 ng/ml	55,1 %	39,2 %	13,6 %	**0,001**
≥3,5 ng/ml	50,5 %	15,8 %	0 %	**0,014**
P	0,597	0,175	0,632	

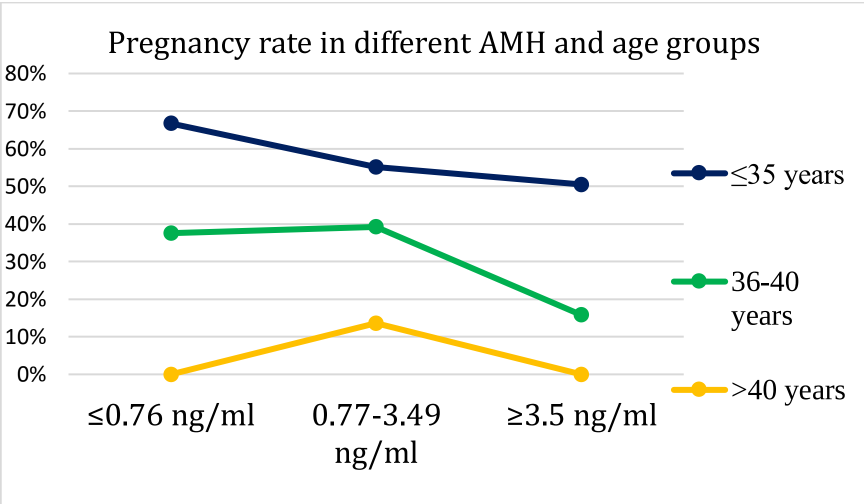

Fig. 6. Pregnancy rates in different AMH and age groups

Table 36 and fig. 6 shows pregnancy rates in different AMH and age groups. Pregnancy rate is high even when AMH is low in women younger than 36 years old. Pregnancy rate is low even when AMH is normal (likely ovarian response to gonadotropin stimulation is normal) in women older than 40 years.
Delivery rates are also significantly decreases with increasing age in all AMH groups (table 37).

Table 37. Delivery rates in different AMH and age groups

AMH	**≤35 years**	**36-40 years**	**>40 years**	**P**
≤0,76 ng/ml	55,6 %	0 %	0 %	**0,009**
0,77-3,49 ng/ml	38,2 %	23,5 %	0 %	**0,001**
≥3,5 ng/ml	38,5 %	5,3 %	0 %	**0,015**
P	0,586	0,078		

Table 38. Miscarriage rate of women who got pregnant after ART

AMH	**≤35 years**	**36-40 years**	**>40 years**	**P**
≤0,76 ng/ml	16,7 %	100 %	-	**0,018**
0,77-3,49 ng/ml	30,6 %	40 %	100%	**0,048**
≥3,5 ng/ml	23,9 %	66,7 %	-	0,104
P	0,646	0,127		

Level of AMH had no significant influence on miscarriage rates in women who got pregnant after ART, but we noticed that in women aged 36-40 years old miscarriage rate was higher in low and high AMH groups than in normal AMH group. Miscarriage rate was increasing significantly with increasing age in low and normal AMH groups (table 38).

Ovarian reserve and likely ovarian response to gonadotropin stimulation can also be measured by level of basal FSH. Fig. 7 shows participants distribution according to FSH. FSH level was 4 - 8,9 IU/L in 80 % (N=461) of women, so the likely ovarian response to stimulation was normal.

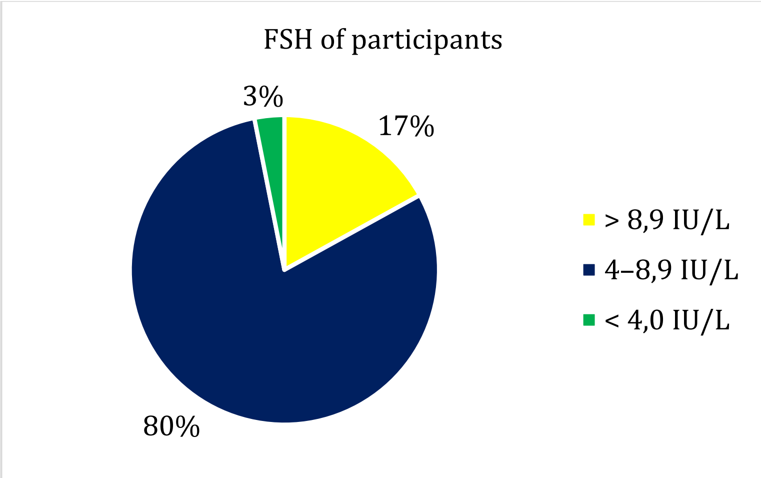

Fig. 7. FSH of participants

Table 39. Pregnancy and delivery rates in different FSH groups

FSH	**Pregnancy**		**No pregnancy**		**Delivery**	
	N	**%**	**N**	**%**	**N**	**%**
> 8,9 IU/L	35	35,7	63	64,3	25	25,5
4-8,9 IU/L	195	42,3	266	57,7	130	28,2
< 4 IU/L	9	50,0	9	50	4	22,2
Total	239	41,4	338	58,6	159	27,6

Table 39 shows pregnancy and delivery rates in different FSH groups. Pregnancy rate is increasing when FSH level is decreasing (likely ovarian response to stimulation is increasing). Highest delivery rate is observed in normal (4-8,9 IU/L) FSH group, but the differences are not statistically significant (p=0,366; p=0,757).

Table 40. Delivery and miscarriage rates in women who got pregnant after ART

FSH	Delivery		Miscarriage	
	N	**%**	**N**	**%**
> 8,9 IU/L	25	71,4	10	28,6
4-8,9 IU/L	130	66,7	65	33,3
< 4 IU/L	4	44,4	5	55,6
Total	159	66,5	80	33,5

Higher miscarriage rate of women who got pregnant after ART was observed in low FSH group, but the differences were not statistically significant (p=0,309) (table 40).

Table 41. Pregnancy rates in different FSH and age groups

FSH	**≤35 years**	**36-40 years**	**>40 years**	**P**
> 8,9 IU/L	49,1 %	32 %	0 %	0,014
4-8,9 IU/L	51,4 %	39,6 %	15,4%	**0,001**
< 4 IU/L	69,2 %	0 %	0 %	0,177
P	0,414	0,575	0,421	

Table 41 shows pregnancy rates in different FSH and age groups. Highest pregnancy rate (69,2 %) was observed in women who were young and had low FSH. Increasing age significantly decreases pregnancy rates in normal FSH group.

Table 42. Delivery rates in different FSH and age groups

FSH	**≤35 years**	**36-40 years**	**>40 years**	**P**
> 8,9 IU/L	38,2 %	16 %	0 %	**0,017**
4-8,9 IU/L	36,4 %	22,8 %	0 %	**0,000**
< 4 IU/L	30,8 %	0 %	0 %	0,657
P	0,881	0,663		

Age had significant influence on delivery rates in high and normal FSH groups. Highest delivery rate was observed in women who where young and had high FSH (table 42).

Table 43. Miscarriage rate of women who got pregnant after ART

FSH	**≤35 years**	**36-40 years**	**>40 years**	**P**
> 8,9 IU/L	22,2 %	50 %	-	0,127
4-8,9 IU/L	29,1 %	42,5 %	100 %	**0,005**
< 4 IU/L	55,6 %	-	-	
P	0,162	0,696		

High miscarriage rate was (55,6 %) observed in women who were young and had low FSH, but differences were not statistically significant. Increasing age significantly increases miscarriage rate in normal FSH group (table 43).

5.8. Multivariate analysis

Logistic regression analysis showed that increasing female age, weight, BMI, waist and hip circumference, WHR, FSH, LH and FAI decreases pregnancy and delivery rates after ART. Increasing female height, AMH, number of oocytes and embryos, AFC, increases pregnancy and delivery rates after ART (tables 44 and 45).

Table 44. Logistic regression for pregnancy rate after ART

Indicator	Pregnancy	No pregnancy	P
	OR (95% CI)	OR (95% CI)	
Age (years)		1.057	0.000
Height (cm)	1.037		0.002
Weight (kg)		1.028	0.000
BMI		1.112	0.000
Waist circumference (cm)		1.014	0.040
Hip circumference (cm)		1.009	0.274
WHR		9.410	0.040
FSH		1.067	0.118
LH		1.009	0.800
E2	1.000	1.000	0.247
Prolactin	1.000	1.000	0.523
Testosterone	1.011		0.688
SHBG	1.003		0.358
FAI		1.255	0.023
AMH	1.016		0.683
2D:4D ratio	1.083		0.979
Number of oocytes	1.037		0.001
Number of embryos	1.087		0.000
Dose of gonadotropins	1.000	1.000	0.001
AFC	1.048		0.026

Table 45. Logistic regression for delivery rate after ART

Indicator	Delivery	No delivery	P
	OR (95% CI)	OR (95% CI)	
Age (years)		1.087	0.000
Height (cm)	1.107		0.000
Weight (kg)		1.028	0.000
BMI		1.125	0.000
Waist circumference (cm)		1.021	0.011
Hip circumference (cm)		1.012	0.163
WHR		24.920	0.011
FSH		1.049	0.293
LH		1.036	0.341
E2	1.000	1.000	0.625
Prolactin	1.000	1.000	0.895
Testosterone	1.014		0.619
SHBG	1.002		0.434
FAI		1.261	0.046
AMH	1.050		0.227
2D:4D ratio	5.343		0.622
Number of oocytes	1.018		0.140
Number of embryos	1.067		0.001
Dose of gonadotropins		1.001	0.000
AFC		1.037	0.099

Principle components factor analysis for women who got pregnant and for women who did not get pregnant after ART revealed that all factors (reproductive and body size) are intertwined with each other: 8-9 factors can be distinguished, but they intertwine with each other and unrelated indicators groups cannot be singled out.

So we can make a conclusion that factors influencing body size and proportion, reproductive possibilities and hormonal balance usually are the same and inseparable (tables 46 and 47).

Table 46. Factor analysis for participants who got pregnant after ART

Rotated Component Matrix								
	Component							
Indicator	1	2	3	4	5	6	7	8
Number of oocytes	0.908			-0.171				
AFC	0.863	-0.116				-0.136		-0.111
LH	0.777	-0.184	-0.113		-0.352	0.139	-0.206	
WHR	0.722	0.145	0.158	0.263	0.16	0.255	0.188	
Number of embryos	0.697	-0.107	-0.228		-0.409	0.135	0.288	
Number of embryos (IVF)	0.595		-0.102		-0.562	-0.391	0.265	
Female weight	-0.197	0.925				-0.139		-0.159
Hip circumference		0.914		-0.101		-0.189		
Waist circumference	0.417	0.834	0.157		0.159			
BMI	-0.303	0.829			-0.165			0.33
FAI	-0.193	0.623	-0.2	-0.23	0.144	0.257	0.211	-0.165
Testosterone			0.891	-0.181				
Prolactin	-0.132		0.86				-0.175	0.262
AMH	0.23	-0.174	0.606	-0.2	-0.177	-0.115	0.495	
FSH		-0.184	-0.151	0.795		0.276	0.226	
Dose of gonadotropins	-0.165	-0.258		0.75				0.211
Progesterone	-0.277	-0.153	0.131	-0.669	0.336	0.176	0.249	0.16
Indication for ART	-0.153			-0.136	0.787		0.245	
Number of embryos (IMSI)			-0.233		0.59	-0.248		0.405
Number of embryos (ICSI)	-0.143	-0.18				0.869	0.101	
2D:4D ratio	0.468			0.288		0.722	-0.127	0.118

Estradiol				-0.224			-0.855	0.149
SHBG	0.437	-0.263	0.224	0.241	-0.256		-0.617	-0.246
Female height	0.108	0.323			0.15	-0.268	0.122	-0.81
Female weight		0.148	0.315	0.183	0.216	-0.122		0.775
% of Variance	18.141	15.795	9.361	8.691	7.948	7.849	7.639	7.475
Cumulative %	18.141	33.935	43.296	51.987	59.935	67.784	75.424	82.898

Table 47. Factor analysis for participants who did not get pregnant after ART

Rotated Component Matrix									
	Component								
Indicator	1	2	3	4	5	6	7	8	9
BMI	0.931			0.139					
Female weight	0.92	-0.115							0.243
Waist circumference	0.886			0.124		0.352			0.112
Hip circumference	0.881	-0.195	0.101	0.196		-0.115	-0.145	-0.109	0.2
SHBG	-0.671	0.177	-0.211	0.187	0.109	0.115		-0.293	-0.12
FAI	0.656								-0.285
Number of oocytes	-0.266	0.896		-0.117				-0.205	
Number of embryos	-0.128	0.856	0.275			0.163	0.259		
AFC	-0.272	0.794			-0.203	-0.147	-0.207	-0.118	-0.15
Number of embryos (ICSI)		0.742	-0.406		0.221	0.113		0.233	
Number of embryos (IVF)		0.169	0.92			0.109		0.12	0.137
Indication			-0.727	-0.319	0.1	0.359		0.11	0.13
Testosterone	0.112		0.59	-0.409		0.296			-0.392
Female age		-0.273		0.818					
Dose of gonadotropins	0.454	0.161	0.218	0.69		0.112	0.211		-0.117
Prolactin				-0.126	0.909	-0.164			
LH	-0.271	0.357	-0.136	0.111	0.672	0.245	-0.156	-0.186	0.247
AMH	-0.13	0.267		-0.27	-0.408	-0.353	-0.174	0.254	-0.226

WHR	0.207	0.247	-0.11			0.829	0.255		-0.112
FSH	-0.408	-0.111	0.442	0.272		0.637	-0.255		
Number of embryos (IMSI)	-0.103			-0.241	-0.32		0.765	-0.237	0.216
Estradiol	-0.185	-0.127		0.211	0.31		0.714		
Progesterone	-0.172	-0.23			-0.114		-0.202	0.88	
2D:4D ratio	0.118	0.468	0.105	0.183		0.159	0.422	0.582	
Female height	0.273	-0.164		-0.186			0.135		0.873
% of Variance	20.045	14.161	9.347	7.653	7.228	7.2	6.895	6.137	5.573
Cumulative %	20.045	34.206	43.553	51.206	58.434	65.634	72.528	78.665	84.238

6. DISCUSSION

Female age is one of the most important factors influencing ART success. Fewer oocytes are retrieved, fewer embryos transferred and significantly lower pregnancy rate is observed in older women (≥ 40 years) after ART treatment (Gomes, Canha Ados et al. 2009, Hourvitz, Machtinger et al. 2009). If older women do get pregnant, the risk of miscarriage is much higher. Ongoing pregnancy rate is inversely proportional to maternal age – increasing maternal age decreases clinical pregnancy rate (McCoy, Nakajima et al. 2009). Mean age (M=33,4 years) of participants of this research was higher than the mean age (M=29,1 years) of delivering women in Lithuania in 2016 (2016). Women who got pregnant and delivered after ART were significantly younger than women who did not conceive after ART. Female age had significant influence on pregnancy, delivery and miscarriage rates after ART. Pregnancy rate (48,8 %) in women younger than 36 years old was more than 2 times higher compared to women older than 40 years old (pregnancy rate 20 %); delivery rate was more than 10 times higher in women younger than 36 years old (33,7 %) compared to women older than 40 years old (2,5 %). Timing is very important, but complex side of infertility treatment. Time has influence on diagnosis, prognosis and success of treatment. Prolonged infertile couple's treatment duration can sometimes force doctors to make wrong and potentially harmful decisions. Female age, time to pregnancy and duration of possible treatment must be taken into consideration, but it is very important not to over treat. Scientific research based dynamic models evaluating probability of natural conception could be helpful in decision making and would allow to avoid unnecessary and expensive treatment (Group 2017).

Body mass index. Obesity lowers the probability of pregnancy after ART. In 2010 study aimed at assessing the impact of female BMI on the success of ART (quality of the embryos received and pregnancy rate) was published in Spain. 6500 ART cycles were analyzed in this study. No significant differences were found in treatment, oocyte fertilization rate, embryo transfer day, mean number of embryos transferred, mean number of surplus embryos, blastocyst transfer rate and cleavage stage embryo quality between obese and normal BMI range women. However, embryo implantation rate, pregnancy and delivery rate was lower in obese women compared to normal BMI range women. Increasing BMI gradually decreases pregnancy and delivery rates (Bellver, Ayllon et al. 2010). Our research showed that women who got pregnant and delivered after ART had significantly lower BMI compared to women who did not conceive after ART. Highest pregnancy (49,3 %) and delivery (32,4 %) rate was observed in normal BMI range group. Pregnancy (20,6 %) and delivery (11,8 %) rates were more than twice lower in obese women group. Losing weight before ART increases chances of live birth (Espinos, Polo et al. 2017). However, not all studies find significant correlation between BMI and clinical pregnancy rate, recommending that BMI should not be a basis for IVF treatment denial (Friedler, Cohen et al. 2017).

Morphological characteristics of female body. WHR >0,80 is associated with lower pregnancy rate after ART, even when adjusted for factors like age, BMI smoking and number of embryos transferred. Central type (android) body fat distribution can have negative effect on pregnancy rate because of a different endocrinological and biochemical environment for the oocyte in the growing follicle, poor quality oocytes and endometrial changes due to hormonal imbalance (Wass, Waldenstrom et al. 1997). We did not find statistically significant differences in pregnancy and delivery rates between different WHR groups, but we noticed the trend that increasing WHR decreases pregnancy and delivery rates and increases miscarriage rate. Thus, the morphological features of the female body undoubtedly play a role in the treatment of infertility.

Ovarian reserve. AFC, AMH and FSH levels correlate with the number of oocytes retrieved and pregnancy rates after ART (Nelson, Klein et al. 2015, Keane, Cruzat et al. 2017). However, not all studies support the prognostic value of these markers (Ashrafi, Hemat et al. 2017). In our research, we found out that mean AFC was significantly higher in women who got pregnant compared to women who did not get pregnant after ART. Mean AMH and FSH was similar in both groups. It is well known that ovarian reserve diminishes with age. As age increases, the number of primordial follicles and AMH level in blood serum decrease. AMH decreases before FSH increases. Therefore, AMH can be seen as an early indicator of ovarian reserve loss (Gomez, Schorsch et al. 2016). According to our research, pregnancy and delivery rates decrease with increasing age even when ovarian reserve is normal. Pregnancy and delivery rates in young women (≤35 years old) was high even when ovarian reserve was low. These findings from our study coincide with data from other studies. Study in Germany (1287 participating women) showed that AMH level has no influence on pregnancy rate after ART in young women (<36 years old) (Gomez, Schorsch et al. 2016). Study in Taiwan revealed that probability of live birth after ART was influenced only by the number of good quality embryos in young women (<35 years old) and in older women results were influenced by age and AMH level (Lee, Liu et al. 2009). It is interesting, that pregnancy rate in low AMH group was higher than pregnancy rate in normal and high AMH groups in young women (≤35 years old). The same trend is seen in study done in Germany. These differences might be due to different indications for ART. In the low AMH groups, ART was usually performed due to decreased ovarian reserve; in the high AMH groups, the most common indication for ART was polycystic ovary syndrome. In the normal AMH group, ART was most often performed due to male infertility, endometriosis, adenomyosis, implantation failure, and other causes (Gomez, Schorsch et al. 2016).

7. CONCLUSIONS

1. Female age is the main and most important predictor of IVF outcome. Increasing female age decreases pregnancy and delivery rates after ART. The best results are achieved in women under 36 years of age.
2. Obesity, especially central type, has a negative impact on pregnancy and delivery rates after ART. Increasing BMI and WHR increases miscarriage rate after ART. Increasing female height increases pregnancy and delivery rates after ART.
3. AMH has no influence on pregnancy and delivery rates in young women (≤35 years old) suggesting AMH level monitoring should not be mandatory in this age group. AMH level can be used as a prognostic factor in determining the probability of pregnancy after ART in women over 35 years old.
4. Pregnancy, delivery and miscarriage rates were similar in the different groups of infertility. Mean AMH was significantly higher in women with male factor infertility than in women with female factor infertility.
5. Factors influencing body size and proportion, reproductive possibilities and hormonal balance usually are the same and inseparable.

REFERENCES

A list of references is provided in the manuscript of the Dissertation.

SUMMARY OF THE DISSERTATION IN THE LITHUANIAN LANGUAGE

LIETUVOS NEVAISINGŲ MOTERŲ POPULIACIJOS BIOLOGINIŲ VEIKSNIŲ DAUGIAMATĖ ANALIZĖ

IŠVADOS:

1. Amžius yra pagrindinis veiksnys, turintis įtakos pastojimo, gimdymo ir persileidimo dažniui po pagalbinio apvaisinimo. Didėjant moters amžiui tikimybė pastoti ir pagimdyti gyvą naujagimį po pagalbinio apvaisinimo procedūros mažėja. Geriausi rezultatai pasiekiami moterims iki 36 metų amžiaus.

2. Nutukimas, ypač centrinio tipo, neigiamai siejasi su tikimybe pastoti ir pagimdyti gyvą naujagimį po pagalbinio apvaisinimo procedūros. Esant didesniam KMI ir JKI didėja po pagalbinio apvaisinimo procedūros pastojusių moterų persileidimų dažnis. Esant didesniam moters ūgiui, didėja pastojimo ir gimdymo tikimybė po pagalbinio apvaisinimo.

3. AMH neturi įtakos jaunų (≤35 metų) moterų pastojimo ir gimdymo dažniui, todėl AMH nustatymas neturėtų būti privalomas tokio amžiaus moterims. Vyresnio amžiaus moterims (>35 metų) AMH gali būti naudojamas kaip prognostinis pagalbinio apvaisinimo procedūros sėkmės veiksnys.

4. Pastojimo, gimdymo ir persileidimo dažnis skirtingose nevaisingumo priežasčių grupėse buvo panašus. Moterų, kurioms pagalbinis apvaisinimas buvo atliktas dėl priežasčių vyro organizme, vidutinis AMH buvo reikšmingai didesnis, nei moterų,

kurioms pagalbinis apvaisinimas buvo atliktas dėl priežasčių moters organizme.

5. Veiksniai, lemiantys kūno dydį ir proporcijas, reprodukcines galimybes, hormonų pusiausvyrą yra tarpusavyje labai persipynę ir jų negalima griežtai vieno nuo kito atskirti.

PUBLICATIONS

ARTICLES PUBLISHED ON THE PRESENT RESEARCH FINDINGS:

1. Zivile Cerkiene, Audrone Usoniene, Andre Amsiejiene, Paulius Sakalauskas, Grazina Drasutiene, Diana Ramasauskaite (2015) Impact of quantitative parameters, such as number of retrieved oocytes, number of transferred embryos and availability of surplus embryos for cryopreservation, on clinical pregnancy rates in ART, Gynecological Endocrinology, 31:sup1, 46-50, DOI: 10.3109/09513590.2015.1086507.
2. Andre Amsiejiene, Grazina Drasutiene, Audrone Usoniene, Janina Tutkuviene, Saule Vilsinskaite, Liucija Barskutyte (2017) The influence of age, body mass index, waist-to-hip ratio and anti-Mullerian hormone level on clinical pregnancy rates in ART, Gynecological Endocrinology, 33:sup1, 41-43, DOI: 10.1080/09513590.2017.1399692.
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SCIENTIFIC PRESENTATIONS ON THE THEME OF THE DISSERTATION:

1. A. Amšiejienė. THE INFLUENCE OF AMH, BMI, WAIST TO HIP RATIO AND 2D/4D RATIO ON IVF SUCCESS. 3rd Annual meeting of Baltic Fertility Society. 20-23 May, 2016. Riga, Latvia.
2. A. Amšiejienė, G. Drąsutienė. THE INFLUENCE OF AGE, AMH, BMI AND WAIST TO HIP RATIO ON IVF SUCCESS. The 3rd International Conference Evolutionary medicine: Pre-existing Mechanisms and Patterns of Current Health Issues; The 14th–19th of June, 2016, Organized by the Faculty of Medicine, Vilnius University and Lithuanian Academy of Sciences.

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