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## **Restorative reproductive medicine for infertility and recurrent miscarriage in the outpatient gynaecological practice in Ukraine**

### **Zastosowanie naprawczej medycyny rozrodu w leczeniu niepłodności i poronienia nawracającego w praktyce ambulatoryjnej opieki ginekologicznej na Ukrainie**

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**Abstract:** Objective: To assess the outcomes of treatment the couples with infertility or recurrent miscarriage with restorative reproductive approach and to identify predictors of success. Methods: It was a retrospective study of 282 married couples, who were included in the program in 2 outpatient gynaecological centers in May 2010 - December 2014. The couples were observed to the end of pregnancy (or pregnancies) or withdrawal from the program. All the couples were taught to track the cycle with the Creighton Model FertilityCare System or the sympto-thermal method, and almost all received additional medical treatment. The main outcome was live birth, the secondary outcomes included conceptions, unsuccessful pregnancies, low birth weight and prematurity. Results: In life-table analysis, the adjusted cumulative proportion of first conceptions for those completing up to 24 months of NPT treatment was 77,7% (crude proportion 47.9%). The adjusted cumulative proportion of live births (included only women whose first pregnancy in the program was successful) was 73.6% (117 births, crude proportion 41.5%). The crude proportion of first live births (124 births, including 7 live births in women whose first pregnancy result was miscarriage) was 44%. Mean time to achieving pregnancy was 8 months (from 1 to 44 month). All the births except one were singleton. There were only 3 preterm births (gestational age less than 36 weeks) with one of them in the mentioned twin pregnancy. Only the babies of these 3 pregnancies were born with weight less than 2500 g.

The favorable predictors of live birth were younger age, shorter time of trying for baby, good compliance, pregnancy in history. The unfavorable were hyperprolactinemia, uterine fibroids, endometriosis, male factor. Conclusion: The outcomes of restorative reproductive treatment the couples with infertility or recurrent miscarriage in Ukraine were comparable to those in Ireland and Canada.

**Key words:** infertility, Naprotechnology, predictors of success, recurrent miscarriage, restorative reproductive medicine.

**Abstrakt:** Cel: Ocena wyników leczenia par z niepłodnością lub poronieniem z zastosowaniem naprawczej medycyny rozrodu, oraz identyfikacja czynników predykcyjnych sukcesu.

Metody: Było to badanie retrospektywne 282 par małżeńskich, które zostały objęte programem w dwóch przychodniach ginekologicznych w okresie od maja 2010 r. do grudnia 2014 r. Pary

obserwowano do końca ciąży lub wycofania się z programu. Wszystkie pary nauczono obserwacji cyklu za pomocą Creighton Model FertilityCare System (CrMS) lub metody objawowo-termicznej i prawie wszystkie otrzymały dodatkowe leczenie. Głównym wynikiem były porody żywego dziecka, wtórne wyniki obejmowały poczęcie, nieudane ciąże, niską masę urodzeniową i wcześniactwo. Wyniki: W analizie *life table* skorygowany skumulowany odsetek pierwszych poczęć dla par na 24 miesiące leczenia wynosił 77,7% (wskaźnik surowy 47,9%). Skorygowany skumulowany odsetek urodzeń żywych (obejmował tylko kobiety, których pierwsza ciąża w programie zakończyła się sukcesem) wyniósł 73,6% (117 porodów, wskaźnik surowy 41,5%). Surowy odsetek pierwszych żywych urodzeń (124 urodzeń, w tym 7 żywych urodzeń u kobiet, których pierwsza ciąża skończyła się poronieniem) wyniósł 44%. Średni czas do zajścia w ciążę wynosił 8 miesięcy (od 1 do 44 miesięcy). Prawie wszystkie porody (oprócz jednego) były pojedynczymi. Były tylko 3 porody przedwczesne (do 36 tygodni), z jednym z nich we wspomnianej ciąży bliźniaczej. Tylko dzieci z tych 3 ciąż urodziły się z wagą mniejszą niż 2500 g. Sprzyjające predyktory żywych urodzeń to młodszy wiek matki, krótszy czas starań o ciążę, rzetelność w wykonaniu zaleceń lekarza, ciąża w wywiadzie. Niekorzystne: hiperprolaktynemia, mięśniaki macicy, endometrioza, czynnik męski.

Wniosek: Wyniki leczenia par z niepłodnością lub nawracającym poronieniem według zasad naprawczej medycyny rozrodu na Ukrainie były porównywalne z wynikami takiego leczenia w Irlandii i Kanadzie.

**Słowa kluczowe:** naprawcza medycyna rozrodu, Naprotechnologia, niepłodność, poronienie nawracające, predyktory sukcesu

### 1. Introduction

In Ukraine, the prevalence of infertility when measuring the inability to conceive after 1 year of attempts is about 15%, which means about one million of married couples, with primary and secondary infertility 47% and 52% respectively (Stockij, 2016). Infertility is about so much more than the inability to conceive, as it influences the health and well-being in different ways. Sustaining a child-wish is more strongly associated with women's long-term mental health than fertility treatment-related factors and parenthood status (Gameiro et al., 2014). Infertility stigma and taboos remains a considerable issue to be addressed. Many experience difficulty discussing infertility with their partner and/or healthcare provider for cultural reasons or due to prevailing perceptions that it is a social, rather than medical, condition (ESHRE, 2017).

In Ukraine, gynaecologist in the outpatient setting is usually the first person to whom most infertile couples will approach for guidance. Usually such patients are looking for a gynaecologist with some experience in treating infertility. However, these couples are usually referred to artificial reproductive technologies (ART) without sufficient investigation and treatment which gives them a chance to conceive. Nevertheless, ART procedures are very expensive, and there is no reimbursement, except the cases of bilateral Fallopian tube blockage or removed both Fallopian tubes. So the financial costs of IVF must be borne by the couple. On the other hand, there are couples that cannot accept ART because of ethic or moral issues. Overall, only 30% of Ukrainian infertile couples come to a doctor, 2-15% of them refer to ART, and only 0,8- 5% achieve success (Zukin, 2016). Besides, ART poses

additional risks for both the mother and her baby (Bewley et al., 2011; Grady et al., 2012; McDonald et al., 2009).

From this perspective the outpatient gynaecologic “primary care” setting is in a unique position to provide comprehensive assessment and treatment of infertile couples. A systemic primary approach to the diagnosis and treatment of infertility and miscarriage can be applied here as attractive alternative.

The restorative reproductive medicine (RRM) is one such medical approach (Stanford, 2019). It is based on precise diagnostic and etiologic treatment a constellation of pathophysiologic conditions leading to infertility. Natural procreative technology (NaProTechnology or NPT) is the first systematic approach of this kind. This approach is based on the Creighton Model FertilityCare System (CrMS) – a system used to identify the fertile days of the menstrual cycle on the basis of standardized cervical mucus observations. The CrMS is allied to other systems known as natural family planning or fertility awareness-based methods (Depares et al., 1986; Ecochard et al., 2001, Fehring 2005). These systems give a woman possibility of prospective identifying the day of ovulation and the most fertile days of menstrual cycle. Women’s systematic vulvar observations from cervical secretions have been directly correlated with the probability of conception (Hilgers TW et al., 1989) Although this purpose can be achieved by commercial ovulation tests, standardized vulvar observation of cervical secretions is one of the most accurate ways to identify the estimated time of ovulation, which is found to occur 3 days before and after the last day of fertile type mucus in 99% to 100% of cycles (Ecochard et al., 2001; Leader et al., 1985; Stanford et al., 2019, 13-17).

Based on the standardized menstrual cycle data available from the CrMS, Dr Hilgers and colleagues have developed a series of medical protocols to evaluate possible causes of infertility, and to apply fertility treatments to enhance the probability of conception in vivo. These protocols are known as *natural procreative technology, NaProTechnology, or NPT* and are described in detail in a textbook published in 2004 (Hilgers TW 2004).

A recent two studies found that NPT practised by trained physicians in general practice in Ireland and in Canada resulted in live birth rates comparable to cohort studies of more invasive treatments (Stanford, Parnell, Boyle, 2008; Tham, Schliep, Stanford. 2012). Our study was conducted to assess the outcomes of NPT treatment in infertility and miscarriage in outpatient gynecologic practice in two cities in Ukraine. We hypothesized that the primary outcome of live births and the secondary outcomes of conceptions and multiple births would be comparable to those in these two studies.

## 2. Methods

This retrospective cohort study took place in outpatient gynaecological practice where patients were seen by 3 physicians gynecologists with specialization in NPT. The patients were referred by centers that teach CrMS or symptom-thermal method of family planning, by other physicians or were self referred. We included all the couples who could benefit from NPT treatment for infertility or recurrent miscarriage from May 2010 to December 2014 (inclusive). The couples were observed to the end of pregnancy (or pregnancies) or withdrawal from the program. The final corrections in the database were made in June 2017, so we had a possibility to learn the final result of all the couples participating in the program.

*Infertility* was defined as inability to conceive for at least 1 year with random intercourse, or for at least 6 months with fertility focused intercourse using the CrMS or other fertility-awareness based system to identify the fertile period of the menstrual cycle. Patients with a history of 2 or more miscarriages were also eligible. We included the couples who had 2 or more visits and at least agreed to begin observations of the cycle. We haven't included the couples who were pregnant at the moment of the 1<sup>st</sup> visit. We haven't offered treatment for those with evident anatomic disorders which we knew couldn't be surgically corrected (severe tubal factor, Asherman's syndrome), menopause and the couples with azoospermia. We excluded patients who failed to complete the initial investigations or return to discuss the results.

Data were extracted from the patient medical records that were maintained by three gynaecologists. Extracted information included data from the initial consultation for infertility or miscarriage, all subsequent follow-up visits and telephone or e-mail contacts. Each included patient was assigned an identification number so only de-identified data abstracted from their medical records were entered into a computerized database. The protocol of the study was approved by the Bioethic committee of the Vinnitsa National Medical University, protocol number 7 of 24.04.2014, in Vinnitsa, Ukraine.

Data abstracted from the medical records included age, number of pregnancies in the lifetime and their outcomes, length of time trying to conceive, gynaecologic and andrologic/urologic diagnoses before and after evaluation, treatment, pregnancies, live births and birth weight, miscarriages or ectopic pregnancies, prematurity, multiple births. The evaluation began with the initial hormonal and other laboratory tests followed by charting the menstrual cycle using CrMS or symptom-thermal method. Then hormonal and ultrasound tests timed to menstrual cycle were performed. Women continued to chart their cycles through their treatment. After evaluation, if indicated, medications were given to correct endocrine disorders (eg., hyperprolactinemia, insulin resistance, PCOS) and/or to increase levels of hormones (eg., micronised (oral or vaginal) or intramuscular progesterone, human chorionic gonadotropin injections, letrozole or clomiphene). Semen analyses were

performed and the male patients were treated for any potential contributing factors or referred to a urologist. Surgical treatment was also obtained by referral if necessary. Treatments were adjusted from cycle to cycle by reviewing the ultrasound series, midluteal estradiol and progesterone levels and response of biomarkers (improving cervical mucus and bleeding pattern). The couples were instructed to use the fertile time for intercourse and were informed that it might take up to 24 months for optimizing their cycles and achieving a successful pregnancy. Given that this study was based on a descriptive analysis of outcomes of an existing practice, we did not conduct sample size or power calculations. The primary outcome was the cumulative proportion of couples experiencing conception or conception leading to live birth, assessed at 6, 12, and 24 months after entering the study. We employed life-table analysis to adjust for dropout from treatment. Crude proportions were also calculated. Proportions of low-birth weight and premature births were also assessed. Statistical analysis was performed using STATISTICA for Windows (StatSoft, USA) version 6.0. A *P*-value of < 0.05 was considered statistically significant. A Kaplan-Meier curve was used to estimate the probabilities of becoming pregnant and giving live birth. Potential categorical predictors were evaluated by Cox's F-test in a Kaplan-Meier model and continuous variables in a Cox proportional hazards regression model. Variables with *p* value ≤ 0.05 at Kaplan-Meier survival analysis were entered into multivariable Cox proportional hazards model to identify the independent predictors of pregnancy and live birth.

### 3. Results

The study cohort consisted of 282 couples who were seen for initial consultation between May 2010 and December 2014 and were qualified for NPT treatment and came to at least 2 visits. Women on average were 29 (21-46) years old, and 182 (64.5%) were nulligravida. Previous live births were at 38 (13.4%), previous unsuccessful pregnancies in 81 (28.5%). Eleven couples (3.9%) had previous unsuccessful ART (IVF or ICSI). The mean time that couples had attempted to conceive was 3 years (from 1 to 20 years) (Table 1).

Table 1. Characteristics of couples beginning treatment

Characteristics	Patients (N=282)
woman's age, years, median (min-max)	29 (21-46)
Years trying for baby, median (min-max)	3 (1-20)
Nulliparous, n (%)	182 (64.5%)
Had previous pregnancy*, n (%)	100 (35.5%)
Had previous live birth, n (%)	38 (13.4%)
Had previous unsuccessful pregnancy**, n (%)	81 (28.5%)
Received previous unsuccessful IVF/ICSI	11 (3.9%)

\* Couples could have multiple pregnancy outcomes

A high proportion of women reported having unexplained infertility (125; 44.3%) and unexplained recurrent miscarriage (15; 5.3%). With evaluation there wasn't any couple with unexplained infertility or unexplained recurrent miscarriage, while 203 (73%) had hyperprolactinemia which included patients with prolactin levels above upper limit or within normal limits but with symptoms of hyperprolactinemia (of them 172 (61%) functional hyperprolactinemia (elevation of prolactin level more than 5-fold in metoclopramide test) and 31 (12%) true hyperprolactinemia (elevated prolactin levels which were not associated with macroprolactin), 265 (94%) disorders of ovulation, 252 (83%) limited cervical mucus. The majority of couples had more than one diagnosis. Also, more women were identified as having PCOS (Rotterdam criteria) (initially 38 (13.5%), after evaluation 104 (38.9%), hyperprolactinemia (initially 22 (7.8%), after evaluation 203 (72.0%), hypothyroidism (TSH elevated above 2,5 mIU/L) (absent as initial diagnosis, after evaluation 30 (10,6%) and thyroid autoimmunity (presence of thyroperoxidase antibodies) (initially 4 (1.4%), after evaluation 29 (10.3%). Interestingly, male factor in the patients before they referred to NPT was present in 51 couples (18.1%) and only 31 (11.1%) after evaluation. This was explained by the fact that the initial evaluation of semen analyses in many cases were based on some other than 2010 WHO criteria. It's worth saying that there wasn't any couple in which male factor was a single diagnosis. Also there were more than one diagnosis in the couples (Table 2).

Table 2. Diagnoses of couples before and after evaluation: N=282, couples could have multiple diagnoses

Diagnostic category	Before evaluation, N (%)	After evaluation N (%)
Unexplained infertility	125 (44,3%)	0 (0)
Unexplained recurrent miscarriage	15 (5,3%)	0 (0)
Hyperprolactinemia*	22 (7.8%)	203 (72.0%)
PCOS**	38 (13.5%)	104 (38.9%)
Thyroid autoimmunity	4 (1.4%)	29 (10.3%)
Endometriosis	20 (7.1%)	21 (7.4%)
Uterine fibroids	9 (3.2%)	11 (3.9%)
Low ovarian reserve	2 (0.7%)	9 (3.2%)
Male factor	51 (18.1%)	31 (11.1%)
Hypothalamic amenorrhea	1 (0.36%)	2 (0.7%)
Disorders of ovulation	21 (7.4%)	265 (94%)
Inflammatory diseases***	28 (9.9%)	17 (6%)
Tubal factor	15 (5.3%)	25 (8.9%)
Hypothyrosis	0 (0)	30 (10.6%)
Limited cervical mucus	0 (0)	252 (83%)

\* Included patients with prolactin levels above upper limit or within normal limits but symptoms of hyperprolactinemia

\*\* Rotterdam criteria of PCOS

\*\*\* Included sexually transmitted diseases, salpingitis, endometritis

All the couples performed observations of the cycles according to CrMS (72%) or sympto-thermal method (28%).

The common treatment given to women included usual fertility drugs (clomiphene, letrozol, human chorioic gonadotropine), a well as medications to enhance cervical mucus (vitamin B6, acetylcysteine, guaifenezine, syrup of plantago or ivy, ampicillin). The most common treatment of primary disorders included prolactin-lowering drugs (bromocriptine, cabergoline, quinagolide), metformin, corticosteroids (dexamethasone or prednizolone) (Table 3).

Table 3. Medical treatment used among women, N=282

Treatment	Couples n (%)
Folic acid, vitamins and minerals	189 (67%)
Luteal progesterone	237 (84%)
Prolactin lowering drugs	179 (63.5%)
Letrozol	114 (40.4%)
Medications to enhance cervical mucus production	84 (29.7%)
Metformin	83 (29.4%)
Human chorioic gonadotropin	40 (14.2%)
L-thyroxin	24 (8.5%)
Corticosteroids	21 (7.4%)
Clomiphene	20 (7.1%)
Antibiotics	17 (6%)

In one case ulipristal was applied in a patient with large myoma who refused from surgery, and one woman received penicillamine for treatment Wilson disease.

About half of the patients (mainly women) had some food program and change of the life style. It included low calorie low carbohydrate diet as well as the food program based on the principles of IgG dependent food intolerance and laboratory diagnostics of specific food antibodies. Surgical interventions included laparoscopy, hysteroscopy and histerosalpingography.

### 3.1. Conceptions and live births

There were 135 (47.9%) clinically recognized conceptions by 32 months after starting treatment (adjusted cumulative proportion was 84.7%). For first conception regardless of outcome, the adjusted cumulative proportion was 77.7% (crude proportion 47.9%). From 11 (3.9%) couples with previous unsuccessful ART (IVF or ICSI) pregnancies were achieved in 3 (27.3%).

Table 4. Cumulative outcomes: conceptions and live births

Time interval (months)	Cumulative withdrawals** from treatment (n)	Conceptions				Live births*			
		Starting at time interval (n)	Cumulative conceptions (n)	Crude cumulative proportion	Adjusted cumulative proportion†	Starting at time interval (n)	Cumulative live births (n)	Crude proportion	Adjusted proportion†
0-3	10	282	13	4.6%	4,7%	282	9	3.2%	3.3%
4-6	39	259	47	16.7%	18,3%	259	41	14.5%	16.3%
7-12	59	186	88	31.2%	39.7%	186	75	26.6%	34,6%
13-18	20	86	120	42.6%	65.1%	86	102	36.2%	58.7%
19-24	7	34	131	46.5%	77.7%	34	113	40.1%	73.6%
24-30	5	16	134	47.5%	82.6%	16	116	41.1%	79.5%
30-36	6	8	135	47.9%	86.1%	8	117	41.5%	83.6%
36-42	0	1	135	47.9%	93.5%	1	117	41.5%	91.8%

\* Live births are assigned the time interval when the conception occurred rather than when the birth occurred.

\*\* Included continuing treatment at the end of study follow-up.

† Adjusted by life-table analysis, where withdrawal or continuing treatment at the end of study follow-up are censoring events.

The adjusted cumulative live birth proportion was 73.6% (117 births, crude proportion 41.5%) at 24 months. Additionally, 7 live births occurred in women whose first pregnancy resulted by miscarriage, and finally there were 124 births with crude proportion 44.0%.

Nevertheless in these cases we included only the first pregnancy in life-table analysis (Figure 1 a,b).



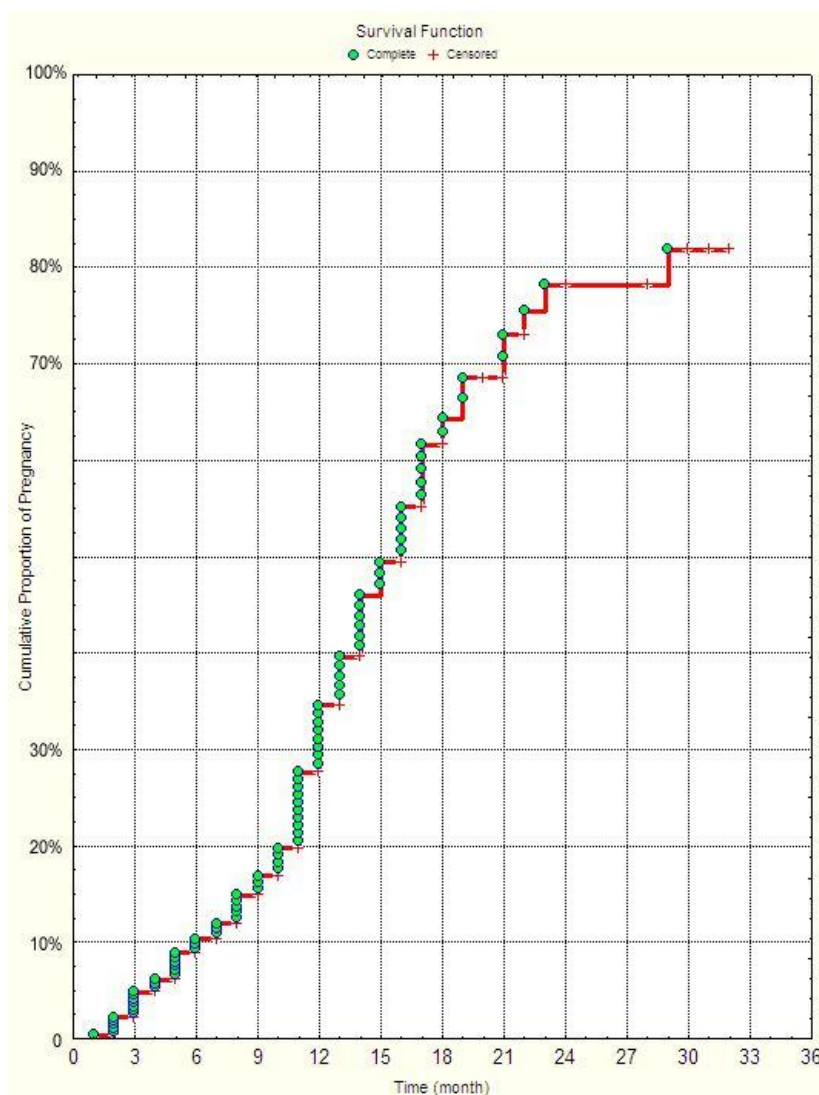


Figure 1. Cumulative rates of conceptions (a) and live births (b): 24 months follow-up of 282 couples

The mean time to any conception was 8 (1-44) months, as to conception leading to live birth. Among couples who conceived 2 (1.5%) used only charting, 123 (91.1%) conceived charting and medical treatment, and 10 (7.4%) after additional surgical treatment.

In Table 5 the outcomes of all live births are shown. There were only one twin but no higher-order births. Almost all babies were born at 37 weeks or later and had birth weight 2500 g or greater. Only 3 pregnancies ended with preterm delivery with 4 babies born prematurely with birth weight less than 2500 g and only one of them with birth weight less than 1500 g. One of them was in a patient with large multiple myomas who had emergency C-section because of fetal distress and preeclampsia. She delivered a boy 1100 g, who was admitted to NICU and discharged from the hospital 2 months after birth in good condition.

Table 5. Outcomes for the first live births, n=117

Outcome	n (%)
Gestation age (weeks)	114 (97.4%)
≥37	
<37	3 (2.6%)
Birth weight	114 (97.4%)
≥ 2500	
1500-2500	2* (1.7%)
<1500	1 (0.8%)

\* including 1 twin pregnancy

The other two patients (of them one with twin pregnancy) had spontaneous preterm birth. None of the babies had birth defects.

Among all the pregnancies there were 5 ectopic (4,2% of all pregnancies). There were 15 miscarriages (12,8% of all pregnancies). Of these 15 couples 7 delivered healthy babies later.

None of the patients experienced ovarian hyperstimulation syndrome. There weren't serious adverse effects of treatment, as well as serious maternal complications.

There were 149 couples who had no conceived . Of those 2 (0,7%) continued treatment and 116 were lost to follow-up and 31 cancelled because treatment was ineffective (after 24 months) or impossible. The reasons they cancelled were: treatment was impossible (the single fallopian tube was removed, advanced age in women at the beginning of treatment and the onset of menopause), didn't wish to continue, wanted to try another treatment or were dissatisfied by treatment. The causes of dissatisfaction with treatment were „treatment lasts too long and costs too much” , „too difficult to observe of the cycles” or desire to achieve pregnancy „naturally” , i.e. without medications.

### 3.2. The predictors of successful pregnancy

Several couple characteristics were associated with the probability of live birth. The increasing age of woman and increasing previous years to conceive were both the strong independent negative predictors of successful treatment (proportional hazard (Cox) regression,  $p < 0.0001$  for both variables). While comparing groups with different age we found significant difference only between groups younger 30 and older 30 year ( $p < 0.0001$ ; Cox's F-test). For women under 30, the adjusted proportion of conception after 24 months was about 87.2%, for the age 31-35 years - 64%, for 36-40 -61.5%, and over 40 years - 81.6% (Figure 2a).

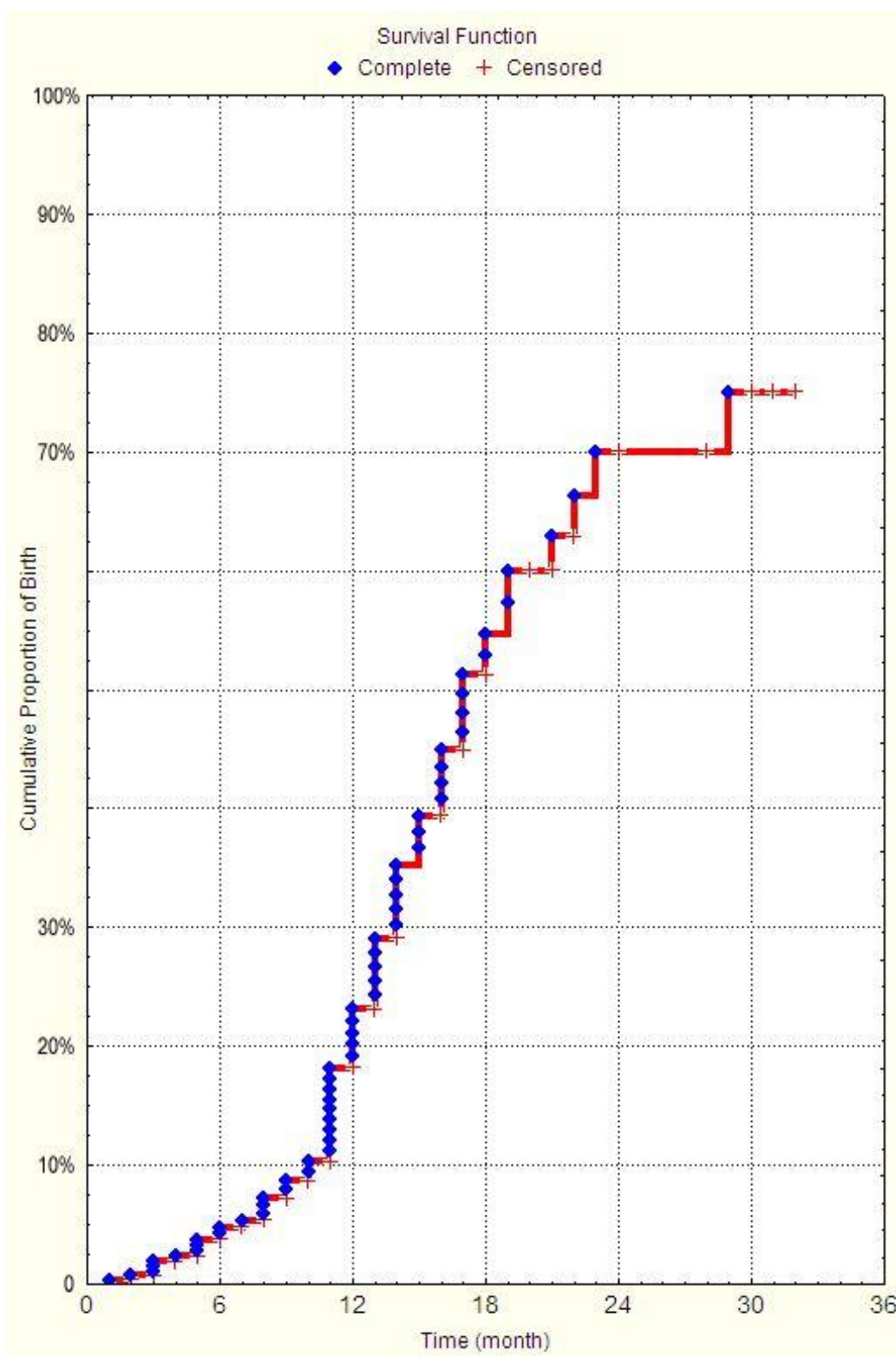


Figure 2a. Cumulative rates of conceptions depending on woman's age (a) and the length of time trying for baby (b): 24 months follow-up of 282 couples

Also, duration of trying for baby were statistically significant independent predictors of getting pregnant and live birth. In the group of couples trying for baby for less than 3 years the prognosis was superb - adjusted proportion of conception after 24 months was

about 95.6%, When this time increased to 4-5 and 6-10 years the proportion of conceptions decreased to approximately 63.8% and 80.7% respectively, but without significant difference between these groups ( $p>0.1$ ; Cox's F-test), and in the group of >10 years it was 44.4% (Figure 2b).

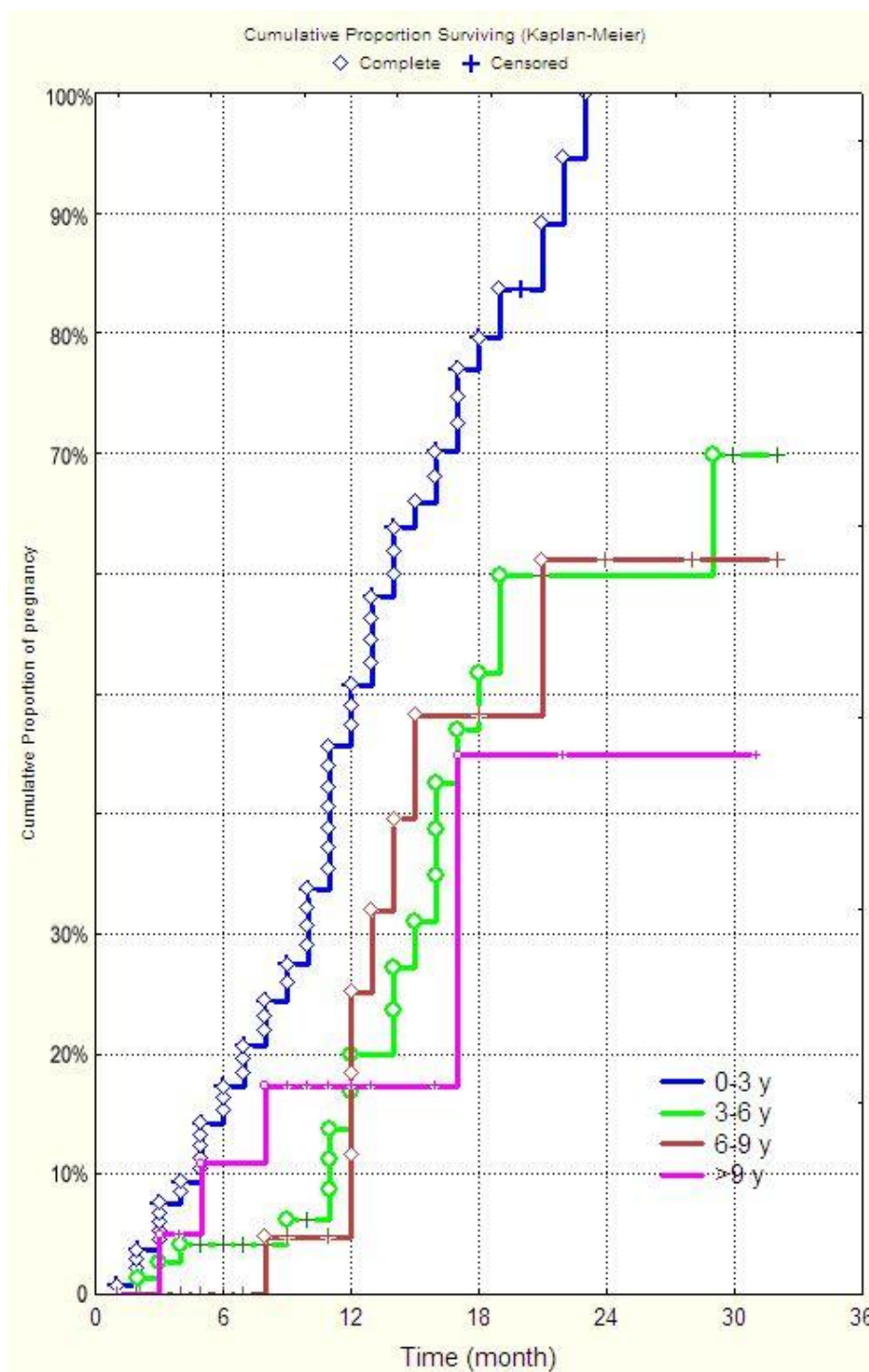


Figure 2b. Cumulative rates of conceptions depending on woman's age (a) and the length of time trying for baby (b): 24 months follow-up of 282 couples

Among the other favorable significant predictors of conception there were pregnancy in history (even unsuccessful), birth in history, recurrent miscarriage, age of the women less than 30 years, and compliance with treatment. The unfavorable predictors - hyperprolactinemia, uterine fibroids, endometriosis, male factor (significant difference between these groups,  $p < 0.05$ ; Cox's F-test). Hypothyroidism, thyroid autoimmunity, and surgery after initiation of treatment had marginally significant difference ( $p < 0.1$ ; Cox's F-test).

All the pregnancies were followed to deliveries, which gave a possibility to study possible predictors of pregnancy loss (miscarriage, ectopic pregnancy, fetal loss). Neither woman's age, nor duration of trying for baby weren't associated with successful pregnancy. Unfavourable predictors included hyperprolactinemia and noncompliance with treatment. The other unfavourable conditions included uterine fibroids, fallopian tubes damage, surgery after beginning of treatment and noncompliance, though a small number of pregnancies in the patients with mentioned conditions made the differences nonsignificant.

## Discussion

In this cohort of couples with infertility or recurrent miscarriage most couples who continued treatment conceived and had live birth within 2 years in life-table analysis. Of those who conceived more than 90% had medical diagnosis guiding medical treatment to enhance conception *in vivo*, and only 2 were able to conceive using only timed intercourse during the fertile phase. Ten couples 10 (7.4%) conceived after additional surgical treatment.

Of all the couples beginning the treatment, included those who dropped out, there were 117 (41,5%) first pregnancies which ended with live birth. Seven couples whose first pregnancy ended with miscarriage had successful subsequent pregnancies during the time of observation, so there were overall 124 births (44% of all the couples). In infertile couples with no treatment,

conceptions within 2 years leading to live births have been found to be about 42% for a population in the Netherlands with a mean female age of 29.1 years and mean duration of infertility of less than 2 years (Snick, 1997). In our cohort where the length of time trying for baby exceeded 2 years in more than 75% of women the results are much better. In the recent German study by Frank-Hermann et al (2017) the cumulative spontaneous pregnancy rate with fertility focused intercourse without any treatment was 38% (95% CI 27-49%) after 8 months of observation. In our study cumulative pregnancy rate for 2 years of treatment was 77.7% and cumulative rates for first successful pregnancies 73.6%, which is about 2 times higher. As the authors haven't given information about the outcomes of pregnancies, simple comparison of the results is difficult. Nevertheless this difference clearly shows the contribution of treatment in solving the problem of infertility.

Compared with outcomes from the recent 2 studies of NPT treatment of infertility and recurrent miscarriage in Irish and Canadian general practice (Stanford et al., 2008; Tham et al., 2012) both crude (41,5% vs 25.5% and 38.0% respectively) and adjusted (73.6% vs 52,8% and 66,0 respectively) cumulative proportion of first live birth after 2 years of treatment are comparable, though closer to Canadian study. This is explained with the fact that our cohort and Canadian cohort are comparable in age, medical conditions, length of time trying for baby and the proportion of women who underwent previous ART (8% vs 3%). Thus, the cohort of our study had comparable initial prognosis as Canadian cohort. Diagnoses and treatment, as well as low rates of multiple births, prematurity and low birth weight were similar in all three studies.

In our study 28% of the couples performed observations of the cycles according sympto-thermal method. "NaProTECHNOLOGY" is a registered trademark of the Pope Paul VI Institute for the Study of Human Reproduction, but according to the author, "it can be freely used by any person or entity so long as its use reflects the medical concepts and values expressed in the textbook" (Hilgers TW, 2004, p. IV ). In the last years the mentioned approach which uses some modalities is usually defined as *restorative reproductive medicine* (RRM) (Stanford, 2019). It's worth saying that sympto-thermal method in our setting had the advantages and shortcomings. First, there is more than 20 years experience and a lot of teachers of sympto-thermal method in all districts of Ukraine, so almost all the patient could find a teacher in the city they live. Besides, symptom-thermal teachers usually referred to us the patients with good skills in this system of observation the cycle. On the other hand, there were only 3 CrMS practitioners in Ukraine up to 2014 and they could to have a limited number of clients, so learning the CrMS was very complicated, especially for the patients who lived far away from medical centers. The main disadvantage of symptom-thermal method is a lack of standartization of mucus observations, so usually women feel difficulties with mucus observation and the records give less information than CrMS. It's worth saying that applying of different natural family planning systems is a usual practice in restorative reproductive treatment. Interestingly, the pregnancy rate was some higher in couples who used symptom-thermal charts, and we explain this by preselection of patients. As we assumed that CrMS is more precise tool, we usually advised symptom-thermal method to the patients with better chances for pregnancy (younger and trying for baby shorter, and for those with good mucus), and in more complicated cases the couples were referred to CrMS practitioner. It's worth saying that serial basal body temperature measurements are accepted as simple and inexpensive method for evaluating ovulatory function, especially in women with subfertility.

It's worth saying that the basal body temperature *per se* and in combination with mucus observations is usually assumed as an important marker of fertility. For example, according to the opinion Practice Committee of the ASRM (2015), „grossly short luteal

phases (<10 days of temperature elevation)" may identify „women with more subtle ovulatory dysfunction". Nevertheless the authors show some skepticism in practical application of the basal body temperature measuring assuming it as unable to „reliably define the time of ovulation" and „tedious". On the contrary Frank-Hermann et al (2017) describe the sympto-thermal method as a useful tool for identifying a fertile window which allows to improve substantially the cumulative spontaneous pregnancy rate. Nevertheless this study was based on education only, without assessment of fertility treatment for the couples with subfertility. As we haven't found any publications about the outcomes of restorative reproductive treatment in the patients using sympto-thermal method, our experience is probably the first description of one.

At last, it should be interesting to compare the results of our study with ART which is assumed as the „gold standard" for treating infertility in the modern world. The data presented at the 35th ESHRE Congress in 2019 showed that IVF and ICSI pregnancy rates have peaked in Europe with 27.1% pregnancy per IVF treatments and 24.3% following ICSI. These figures support the recent trend of a higher success rate in IVF over ICSI. (ESHRE, 2019). European ART treatment outcomes were presented in a retrospective data analysis and summary of the first 15 years of ART activity in Europe (1997–2011) (Ferraretti et al., 2017) which showed that about 6 million of IVF stimulation cycles resulted in approximately 1 million of life births, therefore life birth rate was only 17% per cycle. The cumulative percentage of documented pregnancy losses was 17%. For IUI, the mean pregnancy and delivery rates per cycle were 12.4% and 9.2% in women <40 years and 8.2% and 4.4% in women ≥40 years, respectively. Similarly, in the Collection of European data by the European IVF-Monitoring Consortium (EIM) for ESHRE (2015, published in 2020), EIM has recorded more than 8.8 million treatments with ART leading to the birth of more than 1.6 million infants, which means 18% life birth rate per cycle. The Ukrainian Association of Reproductive Medicine (UARM), which in turn submits data to ESHRE, informs about the overall birth rates for IVF in 2014 with own eggs in Ukraine 38.3% (for patients under 35 years old), 34.4% (for patients aged 35-39) and 26.8% (for patients over 40). According to the data of the Centre for Medical Statistics of the Ministry of Health in Ukraine in 2018 year 27654 ART cycles were performed, 34% of cycles resulted in pregnancies and 27% in live births. As these data show the outcomes of ART procedures per cycle, the simple comparison of them with the results of restorative reproductive treatment is impossible. Such comparison can be made only with the data of studies with cumulative birth rates in ART treatment.

The crude cumulative live birth rates for patients using conventional IVF is in a range of 31-57% for up to 12 cycles (Chambers et al., 2017; Luke et al., 2012; Malizia et al., 2009; Toftager et al., 2017) and are the highest in natural cycle IVF with 65% in women aged 26-34 years and 5% in 43-44 years old (Bodri et al., 2014). Taking into account that real efficiency

of NPT treatment lies somewhere between the adjusted life-table estimates and the crude estimates (Stanford et al., 2008), the success rates in the current study are comparable with this the most effective modality of up-to-date IVF treatment. However, all comparisons must be made cautiously, because the definition of live birth, as well as underlying characteristics of couples which can vary greatly between study populations. Nevertheless the availability of cheaper and less invasive treatments precludes the absolute use of IVF as first-line treatment (Huang et al, 2015). For this reason, certain patient groups with 'good-prognosis' infertility anovulatory infertility, uterine factor infertility can be treated medically or surgically with subsequent spontaneous pregnancy in more than 50% couples. According to the authors, 'good-prognosis' infertility may include unexplained infertility, mild male factor infertility, stage I or II endometriosis, unilateral tubal blockage and diminished ovarian reserve. These data are comparable with the results of our study, and we hope it helps to understand the role of fertility treatment for achieving conception in vivo.

With regards to neonatal outcomes , it is important to note that there were no multiple gestations, and the proportion of premature births was less than 2%. With IVF, multiple gestations are in about 20% of cases (in Ukraine 27%) (Zukin, 2016), and the risks of preterm birth and low birth weight in singletom IVF pregnancy are about 2 times higher than in spontaneous pregnancies (Grady, et al., 2009; Martin, et al., 2017; McDonald, et al., 2009; Soullier, et al., 2011; Woo, et al., 2017).

#### **4. Limitations**

One limitation of this study is limited sample size. Consequently we were able to examine only few group effects (f.e. age, duration of infertility and only several medical conditions). Also, almost half of couples exited the treatment program before a full 24-months course of treatment. This is similar to dropouts in Irish and Canadian NPT studies (Stanford, et al., 2008; Tham, et al., 2012), as well as in IVF studies (Malizia, et al., 2009; Lande, et al., 2011; Luke, et al., 2012; Soullier, et al., 2011).

#### **Conclusion**

The current study showed that restorative reproductive approach in outpatient gynaecological setting resulted in cumulative proportions of live births that were comparable with NPT general practice in Ireland and Canada. The perinatal outcomes (prematurity, low birth weight) were also similar. This approach is positively accepted by patients because the treatment program is minimally invasive and much cheaper than IVF, and that's why it can significantly improve timely access to couples looking for infertility treatment. Further studies are warranted to compare RRM to efficiency of other forms of infertility treatment.



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