

# RESULTS OF TREATMENT OF 412 INFERTILE COUPLES. TWO YEARS OF EXPERIENCE WITH NATURAL PROCREATIVE TECHNOLOGY THERAPY, PRELIMINARY DATA

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**Key words:** *Creighton Model FertilityCare System (CrMS), Natural Procreative Technology (NPT), Infertility, Azoospermia in vitro fertilization.*

## Summary

Infertility affects about 15-20% of couples. In response to this problem in the last years there has been an intense development in diagnostic and therapeutic methods defined as Assisted Reproductive Technologies (ART) connected with an increased risk of iatrogenic disorders in mother and child. The objective of this study was to assess the outcome of Natural Procreative Technology (NPT) treatment in couples diagnosed with infertility.

*Material and Methods.* A total of 412 infertile couples, diagnosed and treated from January 2009 to November 2010 in the NAPROMEDICA center of infertility treatment in Białystok, were included. NPT, a standardized investigation method for diagnosis, and treatment of reproductive function disorders associated with infertility were implemented. The Creighton Model FertilityCare System (CrMS), a standardized method of menstrual cycle monitoring (bleeding and cervical fluid score) was applied. Azoospermia in men and insufficient cooperation in NPT procedures were criteria of exclusion.

*Results.* The average female age was 33.7 years, the mean duration of attempting to conceive was 4.9 years, and 29.4% of couples had previously attempted treatment with assisted reproductive technology (ART). Positive results of pregnancy tests were obtained in 70/412 couples (17.0%); 23.88% in the youngest women subgroup (25–29 years) and 6.52% in the oldest women subgroup (40–47 years). One twin pregnancy was observed

in a group of 70 couples (1.43%) treated with NPT. In the subgroup of couples with conception the mean time from the beginning of NPT treatment to positive pregnancy tests was  $6.6 \pm 5.3$  months (95% CI 5.4 – 7.9 months) including a 3 month diagnostic stage (CrMS).

*Conclusions.* NPT treatment, assessed in a short period of time, may be efficient in achieving a conception in certain couples including those after unsuccessful ART. NPT treatment is associated with rare multiple pregnancies.

## INTRODUCTION

Infertility affects about 15-20% of couples awaiting their offspring, which means that every 5<sup>th</sup> to 6<sup>th</sup> couple is seeking medical help in the field of infertility treatment. Subfertility as a clinical definition generally describes any form of reduced fertility with a prolonged time of unwanted non-conception. Infertility is currently defined as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycle (1-3).

According to the World Health Organization (WHO), a prevalence rate allows infertility to be ranked among social problems. Infertility among married couples is a challenge for modern medicine and healthcare institutions. In the last years in response to the clinical problem of infertility there has been an intense development in methods known as Assisted Reproductive Technologies (ART). At present, married couples suffering from infertility can seek means to conceive in the following ways: monitoring of a woman's natural cycle, pharmacological intervention, i.e. ovulation induction, hormonal support of the second phase of the cycle, and natural procreation. These methods are widely applied in Natural Procreative Technology (NPT). Modern reproductive medicine also implements two other methods. Natural procreation is replaced by artificial insemination, i.e. application of

semen on the cervix or sperm (cells) to the uterus or the fallopian tubes. Another mode of artificial fertilization proposed by modern medicine is in vitro fertilization (IVF).

In the discussion on the safety of these techniques it is emphasized that although the measures taken by gynecologists and obstetricians in this field are highly effective, they frequently expose the patient's health to risk (4). Higher percentages of premature births, low average birth weights, a higher perinatal mortality, a higher percentage of cerebral palsy, and congenital defects are the new issues concerning iatrogenic disorders that accompany ART (5-9). However, the European Society of Human Reproduction and Embryology (ESHRE) recommends that infertility treatment should be concluded with the birth of a healthy child (10). The risk of complications of an in vitro program also includes multiple pregnancies (e.g. twins, triplets or more) (11). Multiple pregnancies are associated with an increased risk of perinatal complications and may be associated with an elimination procedure of an "excessive" number of human embryos (i.e. embryo reduction) (12). This area requires particular

Table 1. Patient characteristics according to age.

	Female	Male
Age, years mean $\pm$ SD	33.7 $\pm$ 4.3	35.7 $\pm$ 6.0
(95% CI)	(33.3 – 34.1)	(35.1 – 36.3)

Table 2. Female subgroups according to age.

Age subgroup	25 – 29 y	30 – 35 y	36 – 39 y	40 – 47 y
Number of women	N = 67	N = 216	N = 83	N = 46
Mean $\pm$ SD	27.9 $\pm$ 1.1	32.5 $\pm$ 1.7	37.3 $\pm$ 1.0	41.6 $\pm$ 1.9

Table 3. The duration of attempting to conceive (in years).

Time	Mean $\pm$ SD	95% CI	Median	Range
Mean $\pm$ SD, years	4.9 $\pm$ 3.3	4.6 – 5.2	4	2 - 21

Table 4. Duration of NPT treatment (in months) in 412 couples registered as patients in NAPROMEDICA.

Patients Groups	Mean $\pm$ SD	95% CI	Median	Range
In the whole group	8.5 $\pm$ 6.3	7.9 – 9.1	8	2 -23
Conception (+) subgroup*	6.6 $\pm$ 5.3	5.4 – 7.9	5	2 -23
Conception (-) subgroup	8.9 $\pm$ 6.4	8.2 – 9.5	8	2 -23

\*Statistical significance difference of  $p < 0.01$  in comparison to the Conception negative subgroup.

observance of ethical principles as well as thorough knowledge of law and security regulations of performing

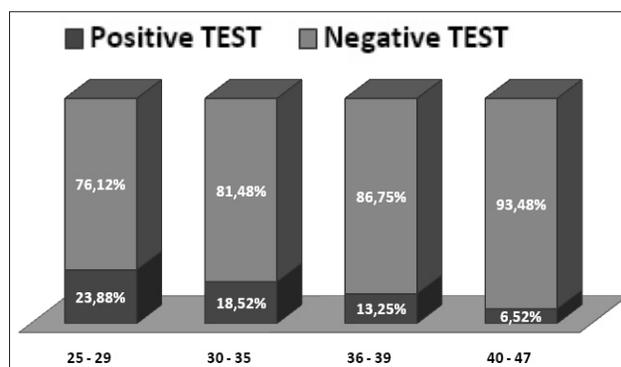


Figure 1. Conception rate (percentage of positive pregnancy tests) in women in four subgroups of age ( $p=0.07$ ).

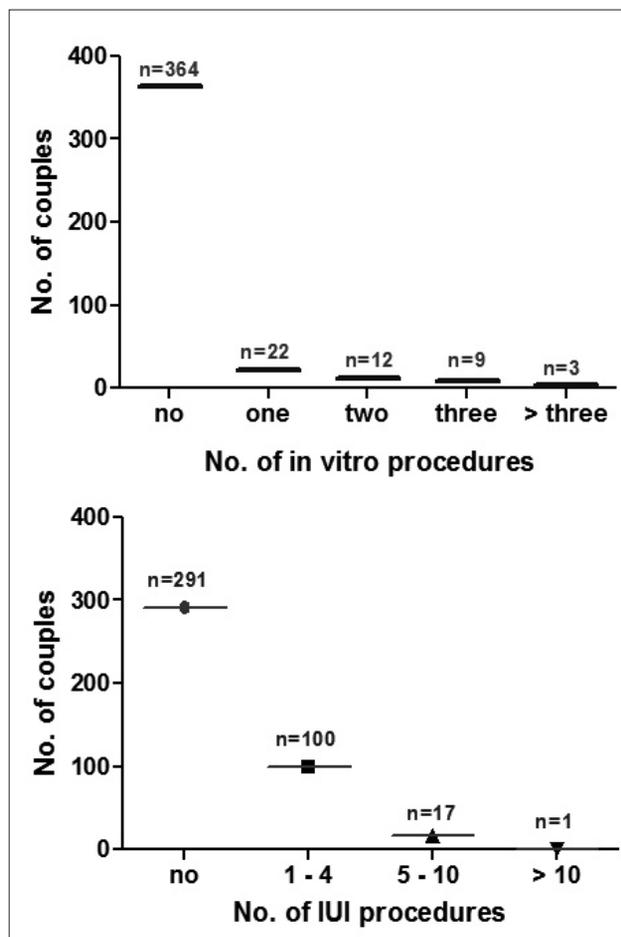


Figure 2. History of previous treatment (in vitro procedures and intrauterine insemination IUI) in couples treated with NPT.

such procedures in accordance with human dignity and autonomy. These expectations are met using Natural Procreative Technology (NPT). NPT is based on an orderly, systematic diagnosis and treatment of systemic as well as gynecological diseases, including fertility disorders, without using contraceptive methods and medications or ART (13). NPT implements actual, cutting-edge knowledge in the field of endocrinology, gynecological surgery, and natural methods of fertility monitoring.

**The objective of this study** was to assess the outcome of Natural Procreative Technology (NPT) treatment in couples diagnosed with infertility.

#### MATERIAL AND METHODS

A total of 412 infertile couples, diagnosed and treated from January 2009 to November 2010 in the NAP-ROMEDICA center of infertility treatment in Bialystok, were included. A detailed medical history including any previous treatment methods such as ART and IUI was collected. Natural Procreative Technology (NPT), a standardized investigation method for the diagnosis and treatment of disorders of reproductive function associated with infertility, as described by Hilgers, was implemented (13). The Creighton Model FertilityCare System (CrMS), a standardized method of menstrual cycle monitoring (bleeding and cervical fluid score) was assessed under the supervision of Creighton Model instructors in all included couples (14). Pre-qualification for CrMS was made by a specialist gynecologist during the first visit to avoid redundant procedures in couples with no medical possibility of conceiving (i.e. azoospermia). Diagnosis of infertility consisted of a series of standard diagnostic examinations including hormone levels (estradiol, progesterone), semen analysis, screening for specific and nonspecific infections (with microbiological examinations), as well as imaging studies such as ultrasound, laparoscopy, and hysteroscopy according to individual indications. After the diagnostic phase, medication treatment was started. This was usually after the minimum three months of CrMS observations giving insight into the quality of the menstrual cycle as defined by cervical mucus characteristics, features of bleeding, and sex hormone levels. Body response to treatment was subsequently monitored using the menstrual cycle scoring system (CrMS). Azoospermia in men was a criterion of exclusion (n=4 couples). All patients who did not sufficiently cooperate in NPT procedures or who withdrew from NPT were also excluded.

#### STATISTICAL ANALYSIS

The Student's t-test was applied to compare variables of a normal distribution. The Mann-Whitney *U*-test was applied to compare variables of non-parametric distribution and the Shapiro-Wilk test to verify the statistical shape of the tested variable distribution. The chi-square test for independence was applied to compare qualitative and categorized variables. Two-tailed  $p < 0.05$  were considered statistically significant. Statistical analyses were performed using GraphPad Prism v 5.03 software and Statistica v 9.0.

#### RESULTS

The average female age was  $33.7 \pm 4.3$  years (Table 1). The age distribution in the studied subgroups of women is illustrated in Table 2. Women aged between 30 years and 35 years were the largest study subgroup amounting to 216 patients. The mean duration of attempting to conceive was  $4.9 \pm 3.3$  years (Table 3).

*The conception rate.* In the whole study group the mean conception rate was 16.99% (70/412 couples); 23.88% in the youngest women subgroup (25 – 29 years) and 6.52% in the oldest women subgroup (40 – 47 years) (Figure 1). 64% of conceptions were in couples with a duration of attempting to conceive between 2 and 5 years, 24% of conceptions were in couples with a duration of attempting to conceive below 2 years, and 12% in couples with a duration of attempting to conceive above 6 years.

*History of previously attempted ART.* In the whole group, 11.7% (n=46) had a previous unsuccessful attempt with in vitro procedures and 29.4% (n=118) were after unsuccessful intrauterine insemination procedures (Figure 2). In the subgroup of couples with positive pregnancy tests, 14/70 (20.0%) couples previously attempted ART, 5 couples with in vitro and 9 couples with IUI.

*Time with NPT treatment.* In the whole study group the mean time of treatment with NPT was  $8.5 \pm 6.3$  months (Table 4). In the subgroup of couples with conception the mean time from the beginning of NPT treatment to positive pregnancy tests was  $6.6 \pm 5.3$  months (95% CI 5.4 – 7.9 months). This time was significantly shorter than the mean time in the subgroup of couples without conception which was  $8.9 \pm 6.4$  months (95% CI 8.2 – 9.5 months) ( $\chi^2$   $p=0.007$ ).

*Multiple pregnancies rate.* One twin pregnancy was observed in the group of 70 couples (1.43%) treated with NPT during a 23 month period.

## DISCUSSION

The main observation from this study is that a mean time of 6.6 months with NPT treatment resulted in conception in 17.0% of woman in the group that had a previous history of attempting to conceive with a mean duration of  $4.9 \pm 3.3$  years. There are some points that should be emphasized with interpretation of these results. One is that this statistical mean of 6.6 months time period includes the first 3 months of diagnostic procedures and CrMS observation and the next mean of 3.6 months is the real time of medical intervention with pharmacological support and lifestyle modification. Another aspect is that conception does not guarantee live birth; such data are not yet available due to this short time period of observation and is why this is presented as a preliminary report. Next aspect is that although it would be optimal to believe that all these conceptions were due to the treatment, spontaneous healing should be also considered as in all forms of infertility treatment. In natural conditions most of the pregnancies occurred in the first six cycles with intercourse in the fertile phase (80%). After that, serious subfertility must be assumed in every second couple (10%) although, after 12 unsuccessful cycles, untreated live birth rates among these couples will reach nearly 55% within the next 36 months (15).

The possibility of conception was found even after unsuccessful ART procedures, including in vitro and IUI (which constituted 20.0% of the couples treated with NPT). This may indicate that reproductive potential was not maximized before ART in these couples. An important advantage of NPT is that it allows avoiding certain adverse health effects inherent to IVF procedures (16-19). Women who undergo in vitro fertilization are, among others, at risk of ovarian hyperstimulation and thrombo-embolic complications (15). They are also at risk of multiple pregnancies and associated perinatal complications (10). To increase their success rate, most IVF centers have indulged in the transfer of multiple embryos resulting in more than half of the children born after IVF originating from multiple gestation pregnancies (e.g. twins, triplets or more)(10).

In this study the rate of multiple pregnancies associated with NPT treatment was 1.43% being comparable to the rate encountered in natural conceptions which amounts to 3%.

Assisted reproductive technologies have helped numerous married couples achieve a long awaited pregnancy. In that case, why are there so many controversies over the in vitro program? It is known that in order to achieve 25-35% effectiveness in an IVF program it is

necessary to conduct intensified ovarian stimulation (10). The average number of oocytes collected nowadays varies between 10 and 15; a large excess considering that only one to three embryos will be transferred. The remaining embryos undergo cryopreservation in order to be possibly "used" in the future. Cryopreservation is a process in which human embryos are at a higher risk of damage or mortality. Transferring those who survive into the uterus is not as effective in achieving pregnancy as transferring "fresh" embryos. This is an ethically negative aspect of the in vitro program. Multiple pregnancies are associated with an increased risk of perinatal complications and may be associated with elimination procedures of "excessive" human embryos (11-12). It could even be claimed that it is also medically unsound, causing the unnatural death of a human being in the embryonic stage of development (20). Selection, i.e. the choice of the two best human embryos, means that the conceived human beings are not equally respected. Human embryos with worse developmental parameters are allocated to the group destined to be cryopreserved, which means that they are put at risk of higher mortality. The conclusion is that the chance to survive is not given equally to all conceived human beings (12).

A new field of issues is created which accompany ART and concern iatrogenic disorders (21). This field requires compliance with ethical principles and thorough knowledge of the law regulating experiments on humans, as well as security rules concerning the realization of such procedures while respecting the autonomy and dignity of a human being (4, 22). Particular responsibility rests upon those scientists who have competence in solving biomedical problems (21).

In NPT a lot of emphasis is laid on the precise determination of the factors that are responsible for infertility and on their correction by means of minimally aggressive therapeutic technologies in order to enable natural conception. The scientists who work in this field of medicine point out that NPT does not tamper with natural procreative mechanisms and protects the relationship of the parents-to-be. Both spouses are involved in the diagnostic stage and especially in CrMS. In NPT, a standardized menstrual cycle observation is crucial for both a physician's medical decision making as well as for a couple's decision about optimal time of intercourse to maximize chances of conception (23-24).

There are some limitations of this study. The main one is that the time period of this study was short and did not allow for gathering of full information on pregnancy outcomes and thus infertility outcomes. The final result of

this study and the time of conception leading to live birth will be published after the required time period for such analyses has passed. Although preliminary, the results obtained should be available as a resource for others to be able to compare to while beginning in NPT.

### CONCLUSIONS

NPT treatment assessed in a short time period may be efficient in achieving a conception in certain couples including those after unsuccessful ART. NPT treatment is associated with a low rate of multiple pregnancies.

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### NATŪRALI PROKREACINĖ TECHNOLOGIJA: 412 NEVAISINGŲ PORŲ GYDYMO PRELIMINARŪS REZULTATAI

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Santrauka

*Raktažodžiai: Kreitono modelis, natūrali prokreacinė technologija, nevaisingumas, azoospermija, apvaisinimas in vitro.*

*Įvadas. Nevaisingumas paliečia 15-20% porų. Pastaraisiais metais šią problemą imta spręsti diagnostikos ir gydymo metodais, apibūdinamais kaip pagalbinio apvaisinimo technologija (angl. Assisted Reproductive Technologies - ART). Šis metodas neretai sukelia riziką motinos ir vaiko sveikatai. Studijos tikslas: įvertinti natūralios prokreacinės technologijos (angl. Natural Procreative Technology -NPT) efektyvumą.*

*Metodika. Nuo 2009 m. sausio iki 2010 metų lapkričio Bialystoko NAPROMEDICA nevaisingumo gydymo centre tirta ir gydyta 412 nevaisingų porų. Joms taikyti natūrali prokreacinė technologija bei standartiniai nevaisingumo diagnostikos ir gydymo metodai. Buvo taikomas menstruacinio ciklo stebėjimas naudojant Kreitono modelį (angl. Creighton Model FertilityCare System -CrMS), kuriame standartizuotai žymimas kraujavimo ir gimdos kaklelio gleivių kitimo pobūdis. Įstudiją neįtrauktos poros, kurių vyrams diagnozuota azoospermija bei poros, nenorėjusios dalyvauti natūralios prokreacijos procedūrose.*

*Rezultatai. Vidutinis moterų amžius buvo 33,7 metai, vidutinis siekimo pastoti laikas- 4,9 metai, o 29.4% porų prieš tai taikytos pagalbinio apvaisinimo technologijos. 70 -čiai moterų iš 412-ies buvo sulaukta teigiamo nėštumo testo (17.0%): 23.88% jaunesnių moterų (25-29 metų) subgroupėje ir 6,52% (40 - 47 metų) subgroupėje. Vienu atveju iš 70-ies (1,43%) užsimezgė dviniai. Pastojusiųjų moterų grupėje vidutinis gydymosi natūralia prokreacne technologija laikas iki teigiamo nėštumo testo 6,6 ± 5,3 mėnesiai (95% KI 5, 4 - 7,9 mėnesiai), įskaičiuojant ir 3 mėnesių diagnostikos (CrMS). tarpsnį*

*Išvada. Natūralios prokreacinės technologijos taikymas kai kurioms poroms gali būti efektyvus, net ir tais atvejais, kai nepadėjo pagalbinio apvaisinimo metodai. Daugiauvaiviai nėštumai pasitaiko retai.*

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Gauta 2011-03-16