Construction of prognostic models of reproductive health of men with chronic inflammation of the urogenital tract

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The objective: to statistically evaluate the effect of chronic inflammation of the urogenital tract, as well as other concomitant factors on reproductive health of men, and also predict the likelihood of being healthy in the future.

Materials and methods. The research is implemented in several successive stages. At the first stage, by means of an expert survey of family doctors, dermatologists and urologists, a system of key indicators for the effects on reproductive health of men was developed, due to the transfer of chronic inflammation of the urogenital tract. At the second stage, the collection of information on key factors of influence through the questioning of men during 2015–2019 by the face-to-face approach during the reception of patients on the clinical bases of the Department of Family Medicine and ambulatory-polyclinic care of NMAPE named after PL Shupik. The survey was attended by 388 patients. In the third stage, on the basis of the established database of interviewed patients, the correlation between the index of reproductive health of men with chronic inflammation of the urogenital tract and the main factors that cause it are established. At the next stage, factor variables have been selected and prognostic models of the probability of decreasing fertility among men who have been diagnosed with chronic inflammation of the urogenital tract have been constructed.

Results. A system of key indicators of the effect on reproductive health of men, as a result of the transfer of chronic inflammation of the urogenital tract is grouped into five blocks: socio-demographic characteristics; diseases of the reproductive system in history; adherence to a healthy lifestyle; peculiarities of sexual life; actual sperm parameters.

The greatest influence on the reproductive health of men who were ill with chronic inflammation of the urogenital tract has demographic characteristics of patients and parameters of sperm. Thus, men over 40 years of age with a pathological morphotype of spermatozoa with a high probability of decreasing fertility in the background or after treating chronic inflammation of the urogenital tract. During the experimental calculations, it has been established that the most appropriate approach in identifying the factors influencing the future of reproductive health of men is the use of linear prognostic models using structural variables. When constructing a prognostic model of reproductive health of men, it is determined that the model is more adequate when combining the factors of each of the five indicator blocks.

By the results of the discovery of the most important factor variables for their further use in the prognostic models of the state of reproductive health of men, a method of stepwise regression with «joining» and «exclusion» has been applied. The greatest influence on the reproductive health of men who were ill with chronic inflammation of the urogenital tract with an acceptable level of significance of the coefficients of the model and its adequacy in general, at the same time, but the set of factor characteristics in them is different. For the convenience of using the results of simulation and unification of treatment approaches for patients, a scale is proposed for assessing the probability of a decrease in the reproductive health of men from chronic inflammation of the urogenital tract.

Key words: family doctor, chronic inflammation of the urogenital tract, reproductive health of men, mathematical modeling.
Построение прогностических моделей репродуктивного здоровья мужчин с хроническим воспалением урогенитального тракта
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Цель исследования: оценка влияния хронического воспаления урогенитального тракта, а также других сопутствующих факторов на репродуктивное здоровье мужчин, а также прогнозирование вероятности быть здоровым в будущем.

Материалы и методы. Исследование реализовано в несколько последовательных этапов. На первом этапе путем экспертного опроса семейных врачей, дерматовенерологов, урологов разработана система ключевых индикаторов влияния на репродуктивное здоровье мужчин после перенесенного хронического воспаления урогенитального тракта (ХВУТ). На втором этапе осуществлен сбор информации о ключевых факторах влияния путем опроса мужчин в течение 2015–2019 годов методом интервьюирования при ведении приема пациентов на клинических базах кафедры семейной медицины и амбулаторно-поликлинической помощи НМАПО имени П. Л. Шупика. В опросе приняли участие 388 пациентов. На третьем этапе на основе сформированной базы данных опрошенных пациентов установле ны взаимосвязи между показателями репродуктивного здоровья мужчин с ХВУТ и основными факторами, его обусловливающими. На следующем этапе выделены факторные переменные и построены прогностические модели вероятности снижения фертильности среди мужчин, больных ХВУТ.

Результаты. Система ключевых индикаторов влияния на репродуктивное здоровье мужчин в результате перенесенного ХВУТ струк тированы в пять блоков: социально-демографические характеристики; болезни половой системы в анамнезе; соблюдение здорового образа жизни; особенности половой жизни; фактические параметры спермы. Наиболее негативное влияние на репродуктивное здоровье мужчин, которые перенесли ХВУТ, имеют демографические характеристики пациентов и параметры спермы. Так, мужчины старше 40 лет с патологическим морфотипом сперматозоидов с высокой вероятностью будут иметь снижение фертильности на фоне или после лечения хронического воспаления урогенитального тракта.

В ходе экспериментальных расчетов установлено, что наиболее приемлемым подходом в выявлении факторов влияния на будущее репродуктивное здоровье мужчин является применение линейных прогностических моделей с использованием структурных переменных. При построении прогностической модели состояния репродуктивного здоровья мужчин определено, что модель является более адекватной при сочетании факторов каждого из блоков индикаторов.

По результатам выявлены наиболее значимые факторные переменные для их дальнейшего использования в прогностических моделях состояния репродуктивного здоровья мужчин применением метод пошаговой регрессии с «присоединением» и «исключением».

Заключение. Предложены две равноценные модели для расчета вероятности снижения репродуктивной способности среди мужчин с хроническим воспалением урогенитального тракта (ХВУТ) с приемлемым уровнем значимости коэффициентов модели и ее адекватности в целом, в то же время набор факторных признаков у них разный. Для удовлетворения результатов моделирования и унификации подходов к лечению пациентов предложена шкала оценивания вероятности снижения репродуктивного здоровья мужчин с ХВУТ.

Ключевые слова: семейный врач, хроническое воспаление урогенитального тракта, репродуктивное здоровье мужчин, математическое моделирование.

RESULTS OF THE STUDY AND THEIR DISCUSSION

The system of key indicators for the impact on men’s reproductive health, due to the transfer of HCTs, is proposed by the authors to be grouped into five blocks:
A. Socio-demographic characteristics;
B. History of the reproductive system;
C. Maintaining a healthy lifestyle;
D. Features of sexual life;
E. The actual parameters of semen.

The main list of potential factor variables included about 35 indicators, which could be the basis for building adequate statistical and mathematical models for assessing men’s reproductive health (Table 1).

Based on the defined indicator system, a survey tool (questionnaire) was developed and used in the patient survey.

Based on microdata surveys, a number of statistical models have been constructed to reflect the relationship between reproductive health indicators for men with CIUT, taking into account a number of demographic, social, medical and lifestyle factors, as well as sexuality characteristics.

The following indicators were used as indicators of men’s reproductive health (dependent variables in the model):
- Proportion of reproducitively healthy males (control group) – males without signs of HCT (about 29% of respondents);
- the proportion of fertile men – those who were ill with CIUT, but the disease did not affect the ability to have children (about 41%);
- the proportion of infertile men – men who have had a decrease in reproductive capacity due to the disease with CIUT (about 30% of persons).

In the course of the experimental calculations, it was found
that the most appropriate approach in identifying the factors influencing the future reproductive health of men is to use linear prognostic models using structural variables.

The general appearance of the model with structural variables is given by the formula:

$$H = b_1 + b_2 + b_3 + \ldots + b_n,$$

where $H$ is the empirical level of reproductive health of men with CIUT;

$b_i$ – binary variables (age, existing illnesses, bad habits, etc.), $i = 1, 2, \ldots, n$;

$\beta_i$ – a free member who has the value of reproductive health of men with CIUT that corresponds to the zero values of all binary variables;

$\beta_i$ – regression coefficients that reflect the influence of the factor variables included in the model (when $b_i=1$) to the empirical level of reproductive health of men with CIUT, $i = 1, 2, \ldots, n$.

It should be noted that in predictive models with structural variables, all factor traits are binary variables, which means that they take values of 0 or 1.

The ability of a model to describe a realistic situation regarding the existence of a relationship between performance trait and factor variables is determined by the adequacy of the model. At the same time, the main characteristics of the model quality are the coefficient of determination $R^2$, $F$ – ratio, $t$ – statistics [8].

The general appearance of the model with structural variables is given by the formula:

$$H = \beta_0 + \beta_1 b_1 + \beta_2 b_2 + \ldots + \beta_n b_n,$$

where $H$ is the empirical level of reproductive health of men with CIUT;

$b_i$ – binary variables (age, existing illnesses, bad habits, etc.), $i = 1, 2, \ldots, n$;

$\beta_i$ – a free member who has the value of reproductive health of men with CIUT that corresponds to the zero values of all binary variables;

$\beta_i$ – regression coefficients that reflect the influence of the factor variables included in the model (when $b_i=1$) to the empirical level of reproductive health of men with CIUT, $i = 1, 2, \ldots, n$.

It should be noted that in predictive models with structural variables, all factor traits are binary variables, which means that they take values of 0 or 1.

The coefficient of determination $R^2$ characterizes the proportion of change in the productive feature (variance of the productive feature), which is explained by the prognostic model. The higher the value $R^2$, the closer the relationship between the resultant and factor traits (the relationship is measured from 0 to 1). $F$ – Fisher's criterion is used to evaluate the significance of differences in variance series variances. If the values of the coefficient of determination $R^2$ and $F$ – Fisher's criterion exceed the corresponding critical values, this is an indication of the significance of the relationship between the resultant and factor traits, and the model is adequate.

$t$ – statistics characterize the degree of significance of individual coefficients for the factor variables included in the model and they are significant if their values exceed the standard error by more than 2 times the module.

When constructing a prognostic model of men's reproductive health, it was determined that the model was more adequate when combining the factors of each of the five indicator blocks.

The analysis of the scatter histograms and paired correlation coefficients ($r$), as well as a series of statistical transformations and derivatives of relative indicators, highlighted 20 indicators that could be used as factor variables to characterize the future reproductive health of men. It should also be noted that for the sake of comprehensive coverage of impact factors, factor variables were selected in such a way as to ensure that all five blocks of indicators are represented.

The following is an example of a list of selected indicators and the corresponding paired correlation coefficients to predict the likelihood of decreased reproductive ability among men with CIUT (by indicator blocks).

| Block Name                               | Key Impact Indicators                                                                 |
|------------------------------------------|---------------------------------------------------------------------------------------|
| A Socio-demographic characteristics      | Age, height, weight, level of education, place of residence, employment, working     |
|                                          | conditions, diagnosis of infertility.                                                 |
| B Diseases of the reproductive           | Prostatitis, sexually transmitted diseases, chlamydia, mycoplasmosis, herpes simplex  |
| system in history                        | virus on the gene of the waist, anomalies of genital development, genital injury.    |
| C Maintaining a healthy lifestyle         | Presence of bad habits (smoking, drinking), frequency of smoking, frequency of        |
|                                          | drinking alcohol, sedentary lifestyle, physical activity, good nutrition, staying in  |
|                                          | stressful situations.                                                                 |
| D Features of sexual life                | Existence of constant sexual partners, frequency of sexual intercourse, physical      |
|                                          | pleasure from sexual intercourse, frequency of cases of premature ejaculation, use of  |
|                                          | the method of «interrupted sexual intercourse», use of means for raising sexual desire, |
|                                          | presence of children.                                                                |
| E The actual parameters of sperm         | The morphotype of sperm, the proportion of leukocytes in sperm, leukocytospermia,     |
|                                          | the presence of pathological forms of sperm.                                          |

Table 1

System of Key Indicators of Impact on Male Reproductive Health Due to Chronic Inflammation of the Urogenital Tract
Given the limitations of the factors that can be included in the model without loss of adequacy parameters, as well as the importance of each of the selected factors, the author has assembled an expert team to discuss key indicators. According to certain blocks of indicators, the expert group identified the main criteria for the study of male reproductive health:

- Age and mass index;
- A history of STDs and prostatitis;
- Physical activity and consumption of alcoholic beverages;
- Regularity of sexual intercourse and absence of children;
- Sperm morphotype and proportion of leukocytes in sperm.

In Fig. 1 shows the indicators that negatively affect the fertility of men in the presence of HRT in anamnesis, in accordance with the degree of their impact according to the estimates of the expert group.

Thus, according to the data presented in Fig. 1. It should be noted that the greatest impact on the negative reproductive health of men with chronic heart disease has demographic characteristics of patients and sperm parameters. Thus, men older than 40 years with a pathological sperm morphotype are more likely to have a decrease in fertility in the background or after treatment with CIUT [5, 13].

As a result of identifying the most important factor variables for their further use in the prognostic models of men’s reproductive health, a stepwise regression method with «joining» and «exclusion» was applied. At the same time, in order to avoid autocorrelation between the factors included in the model, the rules that in the final model should be presented indicators from different blocks are observed.

Based on the results of the analysis, it is determined that the most appropriate models are the interconnections built for the indicator «Share of infantile men» as a dependent variable.

The prognostic model-1 for the likelihood of impaired reproductive ability in men with CIUT: \( H_{ir} \) includes the following variables:

\[ H_{ir} = 0,178 + 0,123 \times b_1 + 0,206 \times b_2 + 0,036 \times b_3 + 0,100 \times b_4 + 0,237 \times b_5 \]

\[ R^2 = 0,827 \quad R^2_{krit} = 0,316 \]

\[ F = 30,6 \quad F_{krit} = 2,8 \]

| Factor variables | Parameter value | Model parameter explanation |
|------------------|-----------------|----------------------------|
| (free member of the equation) | 0,178 \((t=14,6)\) | This is the average likelihood of reproductive decline in men under 40 years of age who have never had prostatitis, are physically active, have children, and leukocyte counts in sperm are in an acceptable proportion |
| \(b_1\) - a man aged 40 and over | +0,123 \((t=7,1)\) | All things being equal, the probability of a reproductive decline for men with a history of 40 years and over is on average 0.123 and is 0.301 or 30.1% |
| \(b_2\) - in the past, a man had contracted prostatitis | +0,206 \((t=4,2)\) | Other things being equal, for men with CIUT who have prostatitis, the likelihood of a decrease in reproduction increases by an average of 0.206 and is 0.384 or 38.4% |
| \(b_3\) - the man does not exercise | +0,036 \((t=1,9)\) | Other things being equal, for men with CIUT who do not exercise, the likelihood of a decrease in reproduction increases by an average of 0.036 and is 0.214 or 21.4% |
| \(b_4\) - man has no children | +0,100 \((t=3,2)\) | All things being equal, for men with CIUT who do not have children at the time of the survey, the likelihood of a decrease in reproduction increases by an average of 0.100 and is 0.278 or 27.8% |
| \(b_5\) - there is a disproportion of leukocytes in semen | +0,237 \((t=5,3)\) | All things being equal, for men with CIUT, semen analysis of which showed a leukocyte disproportion, the likelihood of a decrease in reproduction increases by an average of 0.237 and is 0.415 or 41.5% |
The critical values of the given model quality characteristics correspond to the 95% probability of correlation between performance and factor variables.

Since the actual values of the coefficient of determination of $R^2$ and $F$ – ratio significantly exceed their critical values, there is reason to argue that the relationship between the resultant and factor traits is adequately described by the equation obtained. The proximity of actual $R^2$ to one means that the association between dense traits, factor variables selected, accounts for 82.7% of the variation in the likelihood of reproductive health decline in men with CIUT.

$t$ statistics indicate the significance of regression coefficients. Their values, as well as the interpretation of the model parameters are given in Table 2.

Thus, 25 combinations of variables from possible sets of traits were used to determine the empirical likelihood of reproductive decline in men with HCTF using predictive model-1. A fragment of the feature set is given in Table 3.

In Table 3, the set of traits by number 1 corresponds to the men with the lowest probability of reproductive decline: these are men under 40 (since $b_1 = 0$), who have never had prostatitis (since $b_2 = 0$), are physically active (since $b_3 = 0$), have children (since $b_4 = 0$), leukocyte sperm counts in an acceptable proportion (since $b_5 = 0$). For these men, the likelihood of a decrease in reproduction is 17.8%.

For these men, the likelihood of a decrease in reproduction is 88.0%.

Thus, depending on the set of patient characteristics, the likelihood of decreased reproductive performance among them in the model-1 ranges from 17.8 to 88.0%.

The prognostic model-2 for the likelihood of impaired reproductive ability in men with CIUT $(H_i)$ includes the following variables:

- $b_1$ – body mass index above 29.5 («1» – yes; «0» – no);
- $b_2$ – in the past, a person was ill with STD («1» – yes; «0» – no);
- $b_3$ – daily consumption of alcoholic beverages
- $b_4$ – irregular intercourse
- $b_5$ – pathological morphotype of sperm

| №  | $b_1$ | $b_2$ | $b_3$ | $b_4$ | $b_5$ | $H_{max}$ |
|----|-------|-------|-------|-------|-------|-----------|
| 1  | 0     | 0     | 0     | 0     | 0     | 0,178     |
| 2  | 0     | 1     | 0     | 0     | 0     | 0,384     |
| 3  | 0     | 0     | 1     | 0     | 0     | 0,214     |
| 4  | 0     | 0     | 0     | 1     | 0     | 0,278     |
| 5  | 0     | 0     | 0     | 0     | 1     | 0,415     |
| 6  | 1     | 0     | 0     | 0     | 0     | 0,301     |
| 7  | 1     | 1     | 0     | 0     | 0     | 0,507     |
| 8  | 1     | 1     | 1     | 0     | 0     | 0,543     |
| ...| ...   | ...   | ...   | ...   | ...   | ...       |
| 24 | 1     | 1     | 1     | 1     | 0     | 0,643     |
| 25 | 1     | 1     | 1     | 1     | 1     | 0,880     |

Source: Written by the author.

| Free member of the equation | Parameter value | Model parameter explanation |
|-----------------------------|-----------------|----------------------------|
| (free member of the equation) | 0.187 (t=13.5) | This is an average chance of a decline in reproductive health among men with BMI below 29.5 who have never had STDs, do not drink alcohol daily, have sexual intercourse more than 2 times a month, with no abnormalities in sperm morphotype. |

$b_1$ – a man with a BMI above 29.5 $+0.103$ (t=4.3) Other things being equal, for men with CIUT with a BMI higher than 29.5, the probability of a decrease in reproduction increases by an average of 0.103 and is 0.290 or 29.0%.

$b_2$ – STDs in history $+0.215$ (t=3.0) All things being equal, the likelihood of a decrease in reproductive capacity for men with CIUT who suffer from STDs increases by an average of 0.215 and is 0.402 or 40.2%.

$b_3$ – daily consumption of alcoholic beverages $+0.058$ (t=1.7) All things being equal, for men with CIUT, the daily consumption of alcohol is likely to decrease by an average of 0.058 and is 0.245 or 24.5%.

$b_4$ – irregular intercourse $+0.078$ (t=1.8) All things being equal, for men with CIUT who have irregular sex (2 times a month or less), the likelihood of a decrease in reproduction increases by an average of 0.078 and is 0.265 or 26.5%.

$b_5$ – pathological morphotype of sperm $+0.287$ (t=5.1) All things being equal, for men with CIUT, semen analysis of which showed a leukocyte disproportion, the likelihood of a decrease in reproduction increases by an average of 0.278 and is 0.474 or 47.4%.

Source: Compiled by the authors.
b1 – a man consumes alcoholic beverages daily («1» – yes; «0» – no);
b2 – irregular sexual relations (twice a month and less) («1» – yes; «0» – no);
b3 – morphotype of sperm pathological («1» – yes; «0» – no).

The final look of the model:

\[ H = 0.187 + 0.103 \times b1 + 0.215 \times b2 + 0.058 \times b3 + 0.071 \times b4 + 0.287 \times b5 \]

\[ R^2 = 0.687 \]
\[ R^2_{krit} = 0.306 \]
\[ (F = 28.2) \quad F_{krit} = 2.8 \]

The proposed model is adequate to the actual values of the model’s quality characteristics for 95% probability. The association between the likelihood of impaired reproductive ability among men with CIUT and factor variables is dense and explains 68.7% of the variation in the outcome variable. Another 31.3% of the variation is due to factors not included in the model. The interpretation of model parameter values for factor variables is given in Table 4.

Thus, 24 combinations of variables from possible sets of traits were used to determine the empirical likelihood of reproductive decline in men with CIUT using prognostic model № 2. A fragment of the feature set is given in Table 5.

In Table 5, the set of traits by number 1 corresponds to the men with the lowest likelihood of decreased reproduction: these are men with a body mass index below 29.5 (since \( b_1 = 0 \), who have never had STDs (since \( b_2 = 0 \)), do not drink alcohol daily (since \( b_3 = 0 \)), have regular sexual relations (more than 2 times a month) (since \( b_4 = 0 \)), with normal sperm morphotype (since \( b_5 = 0 \)). For these men, the likelihood of a decrease in reproduction is 18.7%.

The 24 feature set corresponds to men with the highest likelihood of decreased reproductive performance: these are men with a body mass index above 29.5 (since \( b_1 = 1 \), who have had STDs in the past (since \( b_2 = 1 \), who drink alcohol daily (since \( b_3 = 1 \), have irregular (2 times a month and less) sexual relations (since \( b_4 = 1 \), with pathological morph type of sperm (since \( b_5 = 1 \)). For these men, the likelihood of decrease in reproduction is 92.8%.

Thus, depending on the set of patient characteristics, the likelihood of reproductive decline among them in the model-2 ranges from 18.7% to 92.8%.

For convenience of using the results of modeling and unifying approaches to the treatment of patients, a scale for assessing the likelihood of reproductive health decline in men with chronic heart failure has been proposed. The scale provides for the following classification of patients:

- 0.0–0.30 (or 0.0–30.0%) – low probability of reproductive health disorders;
- 0.31–0.60 (or 31.0–60.0%) – the average probability of reproductive health disorders;
- 0.61–0.93 (or 61.0–93.0%) – high probability of reproductive health disorders.

The results of the testing of the scale of assessment based on patient data gave the distribution shown in Fig. 2.

The data presented in Fig. 2. Evidence of sufficiently close patient distributions on the scale of the likelihood of male reproductive health disorders in the presence of CIUT according to the rating scale.
productive health disorders in both variants of the prognostic models (the relationship between the distributions is 0.874). This indicates that, if the necessary information is available, the proposed models can be equally used in the planning of treatment regimens for men with CIUT.

However, it should be borne in mind that Model 1, like Model 2, do not cover the whole set of factors that determine the reproductive health of men with HCT. Recall that model-1 describes 82.7% of the variation in the resultant variable, while model-2 describes only 68.2%. Therefore, the impact of a number of factors is beyond the model. Among other factors, significant influence are other, not included in the model, semen parameters, which should be taken into account comprehensively in determining the treatment regimen of patients. This involves considering both the sperm morphotype and the leukocyte fraction in the sperm.

**CONCLUSIONS**

1. Medical, social characteristics and spermatological data should be included to evaluate the reproductive health of men with a view to comprehensively assessing the reproductive health of men with CIUT.

2. In the practice of the family doctor, it is advisable to use prognostic models of reproductive health disorders for men with CIUT not only for diagnostic but also for therapeutic and prophylactic purposes.

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