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What causes distress in males undergoing infertility work-up?

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Abstract. – OBJECTIVE: This panel study aimed to identify predictors of the risk for depression in involuntarily childless males undergoing fertility work-up.

MATERIALS AND METHODS: A sample of 255 married males aged 22-51 years seeking their first fertility work-up completed the General Health Questionnaire-28 (GHQ-28) at four time-points. They were tested at the baseline, before their initial fertility evaluation (T_1), before their second andrological appointment, two-three months after the diagnostic disclosure (T_2), and before subsequent treatment/follow-up appointments (T_3 and T_4). The timing of assessment was synchronized with respondent's andrological appointments and medical procedures. Binomial logistic regression was applied to develop prediction models for subgroups with the male, female, mixed, and unexplained factors of infertility.

RESULTS: The risk for depression in involuntarily childless males was associated with a constellation of factors, whose importance might vary depending on the factor of infertility. However, the stage of the andrological procedure was found to be the most significant predictor of the risk for depression in the MFI, FFI and Mixed FI respondents with the greatest odds for T_2 and/or T_3.

CONCLUSIONS: The results of the current study have practical implications. They should be considered in support programs for individuals and/or couples with unintentional childlessness. Infertility treatment specialists or other healthcare professionals should be provided education training programs to help them understand how age, permanent residence or education may influence male distress. They should integrate the knowledge into practice so that they can provide adequate emotional support to unintentionally childless males.

Key Words:

Fertility treatment, Involuntary childlessness, Male/psychology, Male's mental health, Masculinity, Patient.

Introduction

Involuntary childlessness (IC) is medically defined as inability to achieve pregnancy following twelve or more months of sexual intercourse without contraception. IC remains a vital public health issue affecting a significant percentage of couples worldwide (ca. 10-20%)[1-4]. Impaired ability to conceive is a crisis situation, which may have a lasting and damaging psychological impact on couples with an unfulfilled wish for a child. A substantial proportion of infertility cases is due to "male factor" infertility. Male factor infertility is most commonly caused by disturbances in the sperm vitality, motility and number of normal sperm. Other reproductive health issues, such as hypospadias, erectile dysfunction or inappropriate frequency and timing of intercourse are less common causes of infertility[1-5]. Research demonstrated that unintended childlessness is a risk factor for clinically significant distress, anxiety and depression both in the affected males and their partners[6-9].

Most previous observations of psychological outcomes of unintended childlessness have been characterized by a cross-sectional design and presented data collected at a certain time-point. These studies have not sufficiently considered the fact that respondent's emotional response to unintended childlessness may fluctuate in the course of work-up or treatment-related events. It should be emphasized that couples who are planning a baby first realize they have difficulty conceiving and assume these may be symptoms of unwanted childlessness. Help seeking is often initiated by the female partners, who schedule an appointment with a fertility specialist to undergo the necessary fertility evaluation. Males, in turn, assume they are fertile because they can produce semen. As a result, males may ignore the need for andrological

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examination and delay their fertility evaluation. Finally, they decide to go through testing under pressure from their female partners or following the gynecologist's referral. Only after both partners have completed the work-up, fertility specialists are able to determine the cause of unintended childlessness in a couple[10].

Then, depending on their diagnosis and fertility status, the couple starts the next stage when they are awaiting pregnancy under their fertility doctor's care. Each of these stages may affect subject's psychological status. Therefore, studies focusing on respondents' emotional status at a single time-point may not sufficiently demonstrate fluctuations in patient's emotional status across the treatment trajectory. The studies so far pointed out factors that may influence the formation, nature, and severity of changes in psychological status of infertile individuals. Patient's psychological status may be affected by the factor of unwanted childlessness, duration of infertility and the length and the type of treatment[6-8,11-19]. One may also note that the studies on psychological outcomes of infertility in females significantly outnumber those focusing on male respondents[6-9,19]. Specifically, research on sociodemographic aspects of female psychological response to infertility treatment have demonstrated that female adjustment to infertility is associated with various sociodemographic characteristics, such as age, socioeconomic status or waiting time to pregnancy[20].

One can hypothesize that factors such as age or waiting time to pregnancy may be associated with psychological status of males with an unfulfilled wish for a child. However, the determinants of male psychological response to infertility are poorly understood[6,18,19,21].

The determinants of psychological distress and risk for depression in unintentionally childless males should be identified for a number of reasons. Firstly, 40-50% of infertile couples cannot conceive due to the male factor. Consequently, males seek medical and psychological help due to fertility issues[22]. Secondly, elevated distress may adversely influence patient's compliance with the treatment plan or treatment persistence and may lead to early termination of treatment despite a fair chance of treatment success[23]. Thirdly, studies in stress endocrinology indicate stress may adversely influence spermatogenesis through the neuroendocrine system thus psychological strain may indirectly compromise the effects of infertility treatment[24]. Finally, elevated distress is associated with an increased risk of depression or suicide[25-27].

Therefore, the current study evaluated determinants of clinically significant psychological distress and the risk of common psychiatric disorders, such as depression in males with unwanted childlessness. Respondents included males with male (MFI), female (FFI), mixed (Mixed FI) and unexplained or idiopathic (UFI) factors of infertility. The study focused on socio-demographic correlates of male distress (i.e., respondents' age, the female partne's age, length of the couple's relationship, having siblings, urban/rural residence, educational status, occupation, financial status, living arrangements). The authors also examined the effect of fertility or relationship characteristics, such as the time interval between the female's and male's fertility evaluation and waiting time to pregnancy (waiting time to the conception of a baby) because these variables may affect distress and risk for depression. The sample included males who sought help of a fertility doctor for the first time. Respondents were examined at four time-points (at the baseline before obtaining the diagnosis, after the diagnostic disclosure and during the follow-up treatment). They were assessed using General Health Questionnaire-28 (GHQ-28). GHQ-28 is commonly used to identify clinically significant distress and above-average risk of depression and other mood disorders. The screening efficiency, validity and reliability of GHQ-28 have been widely examined. What's more, this assessment tool can be repeatedly applied to the same sample of respondents so it can be used in studies that collect repeated measures at several time-points[28-34]. It was hypothesized male distress and risk of common psychiatric disorders, like depression, would be associated with respondents' socio-demographic characteristics (age, educational status, rural versus urban permanent residence, occupation, financial status or living arrangements). It was also speculated that male distress and risk of common psychiatric disorders such as depression would be associated with fertility and relationship characteristics such as waiting time to pregnancy and the time interval between the female's and male's fertility evaluation. Furthermore, the authors hypothesized the importance of predictors of distress in subgroups of respondents with male (MFI), female (FFI), mixed (Mixed FI) or unexplained (UFI) factor infertility may vary, i.e., significant distress and risk of depression may be determined by different independent variables.

Participants

The study included two hundred and fifty-five respondents without a history of a chronic somatic disease or mental health disturbances. Respondents came from a convenience sample of eligible patients seeking their first fertility work-up at an andrological outpatient clinic in Poznan, Poland.

Participant Recruitment

The infertility staff contacted eligible subjects at the reception desk or in the waiting room of the clinic. The staff described the goals of the planned research to them and requested them to participate.

The sample comprised 255 subjects, 70 of whom discontinued participation during the follow-up. One subject returned an incomplete questionnaire, four subjects ended their participation in the study while sixty-five subjects dropped out from treatment. Two hundred and fifty-three respondents completed the testing twice. Two hundred fifteen respondents were administered the tests three times while 185 of them underwent the testing four times. The reasons for leaving the study were the following: 1) subject's spouse became pregnant; 2) the couple's decision to start ART procedure or 3) the couple believed the likelihood of treatment success was poor. Respondent's medical history including their psychiatric history was taken and the information on the female partner's health status was gathered at the first andrological visit. The medical information was updated at the follow-up appointments. Respondents attended the andrological visit along with their spouses. The spouses were routinely asked to undergo the evaluation and provide the results of their fertility examination for diagnostic purposes. Two hundred and forty-eight (97.2%) subjects provided the data on their female partner's reproductive health status at the baseline (T_1). The remaining seven subjects (2.3%) delivered the results of their partner's fertility examination at the second andrological testing (T_2). The data were collected in a way that guaranteed respondent's anonymity.

Design of the Study

This panel study included the baseline evaluation (T_1) and the three subsequent evaluations (T_2, T_3, T_4), which were 2-3 months apart. The timing of psychological examinations was synchronized with respondent's andrological appointments and their medical procedures. The assessments were carried out on the day respondents provided a semen sample for fertility evaluation one day before the andrological appointment. Respondents were administered the testing (1) at the baseline, before the initial fertility testing (T_1); (2) before the second andrological visit, two to three months after diagnostic disclosure when their emotional response to the diagnosis stabilized (T_2); and (3) before the third and the fourth treatment-related or check-up testing appointments (T_3, T_4). The procedures at T_2, T_3 and T_4 were similar as at T_1. This design made it possible to follow respondents and to identify factors associated with significant distress and risk common psychiatric disorders such as depression in males with unwanted childlessness. Respondents were followed across the timeline of events, including diagnostic disclosure and treatment or follow-up appointments.

Measures

All subjects provided their demographic data at the baseline. They also completed the Polish version of the General Health Questionnaire-28 (GHQ-28). This screening tool assesses symptoms of clinically significant distress and an increased risk of developing mood disorders such as depression in health-care settings.

GHQ-28 is a valid and reliable instrument which is well-known for its screening efficiency (the reliability of .78 to .9 and Cronbach's α=.934)[29,30,32-34]. Subjects reported alterations in their mood/behavior over the last four weeks using a four-point Likert scale. Respondents' GHQ score was calculated with the traditional (binary) method (answers "Not at all", and "No more than usual" scored 0, while answers "Rather more than usual" and "Much more than usual" scored 1). A commonly accepted cut-off points of five indicating elevated levels of psychological distress and an increased risk for depression was applied. Then subjects with scores below and above cut-off point were dichotomized as non-cases (GHQ=0) and cases (GHQ=1) respectively. GHQ-28 was developed to explore self-reported variations in subject's psychological status (e.g., somatic symptoms associated with sleep or appetite, self-perceived stress levels, feelings of tension, low mood, self-efficacy, self-esteem and decision-making skills) and not lifelong personal characteristics. Therefore, GHQ was well suited for the purpose of the current study, which focuses on the impact of diagnostic disclosure and treatment or follow-up appointments over time.

All respondents were measured on the following continuous variables: respondent's age, female

partner's age, waiting time to pregnancy, length of the couple's relationship, duration of female's fertility treatment and time interval between female's and male's fertility examination.

To examine the effect of qualitative variables, respondents were divided into subgroups that were based on their characteristics, i.e., having siblings, permanent residence, educational status, occupation, household income per person (financial status), living arrangements.

1. Having siblings: respondents were dichotomized into only children/with brothers and/or sisters
2. Permanent residence: Respondents were dichotomized into a) rural and b) urban residents.
3. Educational status: Respondents were trichotomized into the following subgroups: a) primary school graduates; b) high school diploma holders; and c) university graduates
4. Living arrangements: Respondents were divided into a) individuals living at their parent's home; b) independent renters; c) government housing residents; and d) homeowners.
5. Financial status (household income per person): subjects were trichotomized into the following subgroups: a) individuals with household income per person of ≤1,000 Polish Zl (PLN); b) individuals with household income per person of ≥1,000 Polish Zl (PLN); c) individuals with household income per person of 2,001-5,000 Polish Zl (PLN).
6. Occupation: Subjects were divided into five subgroups: a) farmers (n=33); b) Production workers and craftsmen (n=70); c) Knowledge workers (office clerks, engineers, pharmacists or teachers) (n=68); d) Small business owners and entrepreneurs (n=73) and e) other professions (e.g., musicians or graphic designers) (n=11). (The details on respondent categories and their baseline sociodemographic characteristics are presented in Table I).

In the current study binomial logistic regression was used to test the hypotheses and identify predictors of clinically significant distress and risk of depression for respondents with MFI, FFI, Mixed FI and UFI. The binomial logistic regression models were formulated with GHQ results as a dependent variable and the level of statistical significance set at.05. For all models, the outcome was GHQ result indicating significant distress (GHQ=1).

Table I. Respondents' baseline sociodemographic characteristics.

Statistic	N (%) or M (SD)
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Age	
Respondents	30.24±4.29 years
Female partners	28.42±3.7 years
Educational status	
Primary/lower secondary school graduates (8 years of education	9 (3.6%)
High school graduates (12 years of education completed)	85 (33.3%)
University diploma holders (17 years of education completed)	161 (63.1%)
Permanent residence	
Rural	37 (15 %)
Urban	218 (85%)
Occupation	
Farmers	33 (13%)
Production workers and craftsmen	70 (27.5%)
Knowledge workers (engineers, pharmacists or teachers)	68 (26.6%)
Small business owners and entrepreneurs	73 (28.6%)
Other professions (e.g., musicians or graphic designers	11 (4.3%)
Household income per person (in Polish ZL) n (%)	
≤1,000	33 (13%)
1,001-2,000	164 (64.3%)
2,001-~5,000	58 (22.7%)
Living arrangements	
Living at parent's home	39 (15.3%)
Independent rent	66 (25.9%)
Government housing	39 (15.3%)
Homeowners	111 (43.5%)

First, single-factor logistic regression analyses were performed to find independent variables with a causative effect on the dependent variable. Then the variables with statistically significant unadjusted odds ratios ($p<.05$) were used as covariates to formulate models for each analyzed subgroup of respondents.

Adjusting for Potential Confounders

The effect of independent variables on significant distress and risk of depression in the sample could be confounded by other factors such as the stage of the andrological procedure. Hence, to adjust for the effect of potential confounder, binomial logistic regression was used. First, single-factor logistic regression analyses were performed to obtain unadjusted odds ratios for the association between the stage of the andrological procedure (time-point of testing) and significant distress and risk for depression in the subgroups with MFI, FFI, Mixed FI and UFI. The unadjusted odds ratios for the stage of the procedure were statistically significant in the subgroups of MFI, FFI and Mixed FI. However, the analysis could not demonstrate statistical significance of the odds ratio for the stage of the procedure in the subgroup with UFI. Consequently, the analyzed independent variable (the stage of the procedure) was included as a covariate to formulate the binomial logistic regression models for the respective subgroups of respondents. The statistical analyses were performed using Statistica 13.3[35].

Ethical Approval

Each subject was informed about the purpose and importance of the study, assured of their anonymity and confidentiality. Subjects voluntarily gave their verbal consent to participate. Their consent was not recorded to maintain their anonymity. The investigator also made sure subjects knew they could leave the study at any moment. The research was approved for scientific and ethical integrity by our University's Bioethical Committee (Approval No: 920/14).

Results

Characteristics of the Sample

The investigation included 255 married males with a mean age of 30.24±4.29 years. Two hundred and fifty-four (99.6%) respondents were childless while one respondent had a child from a previous relationship. Respondents' spouses were 21-42 years old with a mean age of 28.42±3.7 years. Two hundred and thirteen (84.3%) respondents had brothers and/or sisters while 42 (15.7%) of them were only children.

The analysis demonstrated there were 76 (29.80%) participants with the male factor of infertility, 80 (31.37%) participants with the female factor, 78 (30.58%) participants with the mixed factor and 21 (8.23%) participants with the unexplained factor of unintended childlessness. Respondents' waiting time to pregnancy ranged from 8 to 24 months (M=14.53±3.17; Me=14) while the duration of their current marriage ranged from one to eleven years (M=2.16±1.02). The time interval between female's and male's infertility evaluation ranged from 0 to 12 months (M=3.45±2.14). The duration of female's infertility treatment in the subgroups with the male, mixed and unexplained factor of infertility ranged from 0 to 10 months (M=1,94; SD=2.26). Detailed sociodemographics are presented in Table I. The data on the prevalence of clinically significant distress and risk for depression in respondent subgroups at subsequent stages of the procedure were presented elsewhere (Citation anonymized).

Predictors of Significant Distress and Increased Risk for Depression (GHQ=1) in Respondents with MFI Across the Timeline of Treatment-Related/Follow-Up Andrological Appointments

Single-factor logistic regression analysis for the MFI subgroup indicated respondent's age, female partner's age, having siblings, length of couple's relationship, permanent residence, living arrangements, stage of the procedure, time interval between female's and male's initial fertility examination and waiting time to pregnancy were characterized by statistically significant unadjusted odds ratios (ORs≠1.00; OR p-values<.05). These variables were included as covariates to build a logistic regression model. Four of the covariates in the model including respondent's age, having siblings, permanent residence and stage of the procedure were characterized by statistically significant adjusted odds ratios (ORs≠1.00; OR p-values<.05).

Significant distress and increased risk for depression in the MFI subgroup was predicted by respondent's age, having siblings, permanent residence, and stage of the procedure. The analysis demonstrated the odds for significant distress and increased risk for depression increased with respondent's age and were greater for rural res-

idents and only children. Additionally, the odds were also related to the stages of the andrological procedure with the greatest odds for T_2 and T_3. The results of binomial logistic regression in the MFI subgroup are presented in Table II.

Predictors of Distress and Increased Risk for Depression (GHQ=1) in FFI Respondents

Single-factor logistic regression analysis of the results in the FFI subgroup identified the following independent variables with significant unadjusted odds ratios (ORs≠1.00; OR *p*-values<.05): permanent residence, educational status, household income per person and stage of the procedure. These variables were included as covariates to develop a logistic regression model. All the covariates in the model were characterized by statistically significant adjusted odds ratios (ORs≠1.00; OR *p*-values<.05). Significant distress and an increased risk for depression in the FFI subgroup were predicted by permanent rural vs. urban residence, educational status, household income per person and stage of the andrological procedure. The analysis demonstrated the odds in FFI respondents were greater for rural residents who were high school graduates and university diploma holders with the greatest odds for respondents with a university degree. The analysis indicated good financial status increased the odds for distress and risk for depression. Furthermore, the odds were also related to the stages of the andrological procedure with the significantly greater odds for distress and increased risk for depression at T_3 and at T_4. The results of binary logistic regression for the FFI subgroup with dichotomized significant distress and increased depression (GHQ=1) as the dependent variable are presented in Table III.

Predictors of Significant Distress and Increased Risk of Mental Disorders (GHQ=1) in Mixed FI Respondents

Single-factor binomial logistic regression analysis of the outcomes in the Mixed FI subgroup demonstrated educational status, duration of female's treatment and stage of the procedure were characterized by statistically significant unadjusted odds ratios (ORs≠1.00; OR *p*-values<.05). These variables were included as covariates to build a logistic regression model. Adjusted odds ratios were statistically significant for all the three covariates in the model (ORs≠1.00; OR *p*-values<.05). Significant distress and an increased

Table II. Binomial logistic regression for predictors of significant distress and increased risk for depression (GHQ=1) in the subgroup with male factor of unintended childlessness (MFI) .

Covariate	level	95%CI low	95%CI high	OR *p*-value	Adjusted OR
Respondent's age	One year increase*	.018	.448	.034	1.262
Female partner's age	One year increase	-.379	.073	.185	.858
length of couple's relationship	One year	-.184	.695	.254	1.292
Having siblings	Only children	Level of reference			
	with brothers/sisters**	-2.245	-0.556	.001	.246
Permanent residence	rural	Level of reference			
	urban*	-4.451	-.267	.027	.094
Living arrangements	Living at parent's home	Level of reference			
	Independent rent	-1.265	0.949	.779	.854
	Government housing	-.227	2.165	.112	2.635
	Homeowners	-.391	1.709	.219	1.933
Stage of the procedure	T1	Level of reference			
	T2**	2.427	4.670	0.000	34.761
	T3**	1.535	3.870	0.000	14.923
	T4**	0.751	3.172	0.001	7.110
Time interval between female's and male's initial fertility examination	One month*	-.152	0.346	0.445	1.102
Waiting time to pregnancy	One month	-.048	.312	.151	1.141

note: * OR *p*-value <.05 **OR *p*-value <.01.

Table III. Binomial logistic regression for predictors of significant distress and increased risk of mental disorders (GHQ=1) in the subgroup with the female factor of unintended childlessness (FFI).

Covariate	level	95%CI low	95%CI high	OR *p*-value	Adjusted OR
Permanent residence	rural	level of reference			
	urban**	-4.526	-1.289	.000	.055
Educational status	Primary/lower secondary school graduates	level of reference			
	High school graduates*	.741			
	6.312	.013	33.997		
	University diploma holders**	1.268	6.745	.004	54.959
Household income per person (in Polish ZL)	≤1,000	level of reference			
	1,001-2,000*	.561	4.456	.012	12.288
	2,001-~5,000**	1.381	5.334	.001	28.714
Stage of the procedure	T1	level of reference			
	T2	-.282	1.543	.176	1.878
	T3**	.872	2.636	.000	5.778
	T4**	.372	2.192	.006	3.604

note: * OR p-value <.05 ** OR *p*-value <.01.

Table IV. Binomial logistic regression for predictors of significant distress and increased risk of mental disorders (GHQ=1) in the subgroup with the mixed factor of unintended childlessness (Mixed Fi).

Covariate	level	95%CI low	95%CI high	OR *p*-value	Adjusted OR
Educational status	Primary/lower secondary school graduates	level of reference			
	High school graduates**	-6.600	-1.722	.001	.016
	University diploma holders*	-5.462	-.676	.012	.046
Stage of the procedure	T_1	level of reference			
	T_{2**}	2.261	4.187	.000	25.134
	T_{3**}	1.537	3.461	.000	12.170
	T_4	-.338	1,832	.177	2.111
Duration of female's fertility treatment	One month*	-5.462	-.676	.012	.046

note: * OR *p*-value <.05 ** OR *p*-value <.01.

risk for depression in this subgroup were predicted by educational status, duration of female's treatment and the stage of the andrological procedure. The odds for significant distress and risk for depression in this subgroup were inversely associated with duration of female's fertility treatment. Additionally, the odds were greater for respondents with primary/lower secondary education. The odds were also associated with the stages of the andrological procedure with the greatest odds for T_2 and T_3. The results of binary logistic regression for respondents with the mixed factor of unintended childlessness are presented in Table IV.

Predictors of Significant Distress and Increased Risk of Mental Disorders (GHQ=1) in Respondents with the Unexplained Factor of Unintended Childlessness (UFI)

Single-factor logistic regression analysis could not determine any significant association between the analyzed independent variables and the outcome variable in respondents with unexplained factor of unintended childlessness (OR *p*-values≥.05). Consequently, the logistic regression model for this subgroup could not be formulated.

Discussion

Unintentional childlessness remains an important medical issue affecting a marked percentage of males worldwide. Males can be affected by infertility in many ways: they may be diagnosed with infertility themselves, they may be a partner of an infertile woman, they are a part of a couple with combined (mixed) male and female factors of infertility or the causes of the couple infertility remain unexplained[6]. Males and females from couples who are planning to have a baby differ in their approach to difficulties getting pregnant. Women who are trying to conceive, track their fertility and may quickly assume they are infertile because they cannot achieve pregnancy despite regular intercourse. They decide to see a fertility doctor and start the diagnostic process at the slightest hint they are infertile. Males, in turn, often start the diagnostic process much later. They make up their minds to begin fertility work-up under pressure of their female partner/wife or her fertility doctor. Men also postpone their work-up if their partners are subfertile and are undergoing treatment themselves. Most men believe they must be fertile because they associate fertility with the production of ejaculate during intercourse[10]. Several publications have indicated unwanted childlessness may adversely influence male mental health and well-being. To add, infertility, especially if the male factor is present, has been shown to be a risk factor for depression, anxiety and distress both in the affected males and in their spouses[6,7,13-15,36]. The authors of the current investigation used a fertility-specific questionnaire (FertiQoL questionnaire) to assess the effect of diagnostic disclosure on male emotional status, physical health, and marital relationship. Respondents' average FertiQoL scores reached peak values at the baseline before the fertility work-up and then significantly decreased after the diagnostic disclosure. The impact of diagnostic disclosure on emotional, physical, and marital well being as measured by the Emotional, The Mind-Body and The Relational subscales of FertiQoL was particularly marked if the reproductive failure was due to male or combined male and female factor (citation anonymized). Conversely, respondents' scores in the social domain of FertiQoL also peaked at the baseline and remained stable after the diagnostic disclosure. However, these scores significantly declined in the follow-up (at T_3). These findings revealed that continual infertility treatment could be associated with a distinct decline in patients' social functioning (diminished perceived social support, increasing feelings of social isolation and/or inability to meet social expectations relating to childbearing). Interestingly, the analysis could not indicate any statistically significant relationship between semen quality and various domains of FertiQoL. This finding may suggest the disclosure of male factor of unintended childlessness may be more meaningful than being informed about one's poor semen quality (citation anonymized, in preparation). Previous investigations indicated distress and well-being in unintentionally childless males were affected by a number of factors such as duration of infertility, the length or the type of treatment (e.g., subjects were assessed before initiating, while undergoing or after they have completed assisted reproductive technology treatment procedure)[4,7,8,11,16,19,38,39].

However, several questions related to the course and determinants of male distress and psychological status of males undergoing fertility procedures have not been sufficiently elucidated.

To our best knowledge, this is the first investigation that utilized a panel design to evaluate determinants of significant distress and increased risk of depression in males undergoing fertility work-up and/or treatment. Study participants were assessed at four subsequent time-points. They were assessed (1) at the baseline, before diagnostic disclosure of their fertility status (T_1); (2) before the second andrological visit, two-three months after they had learned their role in previous reproductive failure when their emotional response to the diagnosis stabilized (T_2,) and (3) before the third and the fourth treatment-related/check-up testing appointments (T_3 and T_4). The time-points of psychological testing were strictly related to medical appointments because psychological testing was carried one day before respondents' scheduled andrological appointment. The study analyzed the effect of sociodemographics such as (both respondent's and the female partner's) age, urban vs. rural permanent residence, educational status, occupation, financial status (income per person in the family) or living arrangements. The analysis also considered other determinants including time elapsed (time interval) between the female's and male's fertility evaluation and waiting time to pregnancy (waiting time to the conception of a baby).

The study reported the odds for significant distress and risk for depression in individuals with MFI in the sample increased with respondent's age. This finding is comparable to the outcomes of Huppelschoten's investigation[40]. Huppelschoten's

study[40] identified age as a predictor of quality of life and emotional status of males with involuntary childlessness. In contrast, there were studies which produced different results. Patel et al[15] and Yang et al[8] could not indicate the association between age and mental health outcomes in undesirably childless males. The discrepancy likely results from the fact that Patel et al[15] and Yang et al[8] recruited younger respondents, e.g., most participants of Yang et al' study[8] were younger than ours. These findings may imply that despite a relatively short period of conception, participants were under pressure of time, and were aware of decreasing sexual stamina and age-related fertility decline[41-43]. The current analysis also seemed to indicate that rural respondents with MFI and FFI had greater odds for clinically significant distress than the urban residents. This result is consistent with the outcomes of previous investigations, e.g., urban male participants of Dong and Zhou's study[37] had a markedly higher fertility quality of life than their rural counterparts. The results may be explained by cultural attitudes and beliefs related to paternity and childbearing. One may suggest here that producing a biological child of one's own has a high priority for rural residents because many of them own a farm, so it is important for them to produce an heir. Dong and Zhou[37] also suggested urban-rural FertiQoL differences were related to the differences in the cognition of children and the attitude to having children. Furthermore, values related to having biological children may be stronger and are more consistently transmitted to younger generations in rural communities. Dong and Zhou[37] accentuated that rural couples have poor access to reliable sources of state- of -the - art knowledge on fertility issues. Consequently, they have to put more effort into seeking medical therapy as infertility clinics or assisted reproduction technology institutions are located in urban areas.

It is worthwhile to note that being an only child predicted significant distress in MFI participants. This finding may be attributed to the fact that respondents were aware of expectations their own parents may place on them. Becoming a grandparent is often perceived as an essential milestone and a crowning life achievement for parents of adult children so they may openly express their willingness to become grandparents. Consequently, only children participating in our study experienced distress because they could not live up to their own parents' expectations and believed they were responsible for the problem[44].

The study also analyzed the association between respondents' distress and risk for depression and their educational status, financial status (income per person in the family) and occupation. The role of these variables has been examined before. Dong and Zhou[37] demonstrated higher net family monthly income, educational status and being employed were related to better FertiQoL in Chinese males with unwanted childlessness. Similarly, Sehhatie et al[45] indicated monthly self-sufficiency wage and occupational status predicted perceived stress among male subjects from undesirably childless couples. To add, Koochaksaraei et al[21] indicated low educational status and insufficient income were related to impaired social functioning and depression in males with unintentional infecundity. In contrast, our study indicated FFI respondents with high income had greater odds for significant distress and risk for depression than participants of lower financial status. These results may be explained by Maslow's hierarchy of needs. High-earning participants of the study have achieved economic well-being and professional stability, so they are ready to pursue the self-actualization needs. They may think becoming a parent and raising a baby could be another step to living a happy and fulfilling life, but they cannot achieve this life goal at the moment[46].

The results of the present study demonstrated that longer waiting time to pregnancy (longer duration of infertility) decreased the odds for distress and risk for depression in respondents with FFI. The most likely explanation of these outcomes could be that males with longer waiting time to pregnancy were transitioning from attempting conception to adoption as a means to becoming parents. The effect of duration of infertility was recently investigated by Jamil et al[47]. They found longer duration of infertility predicted lower self -esteem in on males with an unfulfilled wish for a child. However, Jamil's results pertained to males with the male factor of infertility.

The present investigation evaluated the association between infertile male's educational status and clinically significant distress. The effect of educational status on mental health outcomes in individual with unintended childlessness has been analyzed before[48,49]. Jamil et al[47] found higher educational status was associated with lowered self -esteem in males with male factor infertility. In contrast, Yang et al[8] could not find any significant association between educational attainment, depression and anxiety in infertile males living in

China. In our study, educational status predicted clinically significant distress and risk for depression in respondents with FFI and Mixed FI. The results indicated the odds for significant distress and risk for depression were greatest in Mixed FI respondents with a primary/lower secondary educational status. This finding may come from the fact that individuals with low educational status are more likely to be influenced by ingrained beliefs linking sexuality and fertility due to probable gaps in their knowledge on sexuality and reproductive health. Simultaneously, higher educational attainment (university degree) predicted distress and risk for depression in participants with the female factor. This finding can be linked to the fact that university-educated individuals may better comprehend and realistically assess their situation. Still, one can suggest here that the standard of ideal manliness is resistant to change and cannot be easily affected by knowledge passed on through education. More research is necessary on the effect of knowledge passed on through education on intrinsic standards of ideal manliness[50].

The analysis could not indicate any associations between subjects' distress and risk for depression and their occupation. Based on these results, one cannot assume this agent does not affect respondent's distress at all. However, the influence of occupation is less evident than the effect of age, income, permanent residence or educational status.

It should be mentioned that the effect of independent variables on the dependent variable in the sample could be confounded by other variables which were not considered in the study. The previous study with the same sample of participants indicated respondent's distress and risk of depression were significantly associated with the stage of the andrological procedure (time-point of testing). Therefore, to adjust for the confounding impact of these variables on the results of binomial logistic regression analysis, they were included in the binomial logistic regression analyses. The results denoted the factor of unintended childlessness played a causative role in distress and risk of depression of males who participated in the study. Participants with the male and mixed factors of unintended childlessness were most likely to be at risk. The odds were smaller in the FFI subgroup and the smallest in individuals with the unexplained factor. The findings revealed the odds for distress and risk for depression in subjects with MFI significantly increased after the diagnostic disclosure of the factor of infertility. The odds for distress at T_2 were 34 times greater than at T_1 (the baseline assessment). As for the Mixed FI subgroup, the odds for distress and the risk for depression increased at T_2 and were ~25 times greater than at the baseline evaluation and then decreased at T_3. In contrast, the odds for distress and the risk for depression in FFI respondents remained stable at T_1 and then significantly increased at T_3. The odds decreased at T_4 but were significantly greater than at the baseline evaluation (T_1). These results suggest the factor of unintended childlessness and the stage of the procedure remained the most important factors associated with significant distress and risk for depression in males participating in the investigation.

Finally, a number of important limitations need to be considered. The present study could not identify any significant association between the independent variables and distress and increased risk for depression in respondents with UFI. Consequently, a statistically significant logistic model for predictors of distress and increased risk of depression in this subgroup could not be formulated.

It should be pointed out that our previous analysis in the same sample of respondents (Citation anonymized) demonstrated the UFI subgroup was characterized by a relatively low baseline percentage of distressed respondents. To add, the analyzed percentage remained stable because significant changes in the percentage of significantly distressed UFI respondents could not be determined at T_2, T_3 and at T_4. However, the distress in this subgroup could be associated with other factors, which were not considered in the present analysis. Other limitations stem from the fact that the study was retrospective. Furthermore, subjects were private patients from one outpatient clinic and covered the costs of andrological procedures themselves. However, the results of the current study have practical implications and should be considered in patient-focused support programs for individuals and/or couples with unintentional childlessness. Infertility treatment specialists should be provided evidence-based education and training programs to help them understand how age, residence or education may influence male infertility-related distress. Reproductive healthcare professionals should integrate the knowledge into practice so that they will be able to provide adequate emotional support to males treated for unintentional childlessness.

Conclusions

Significant distress and increased risk for depression in the MFI subgroup was predicted by

respondent's age, having siblings, permanent residence and stage of the andrological procedure.

Significant distress and an increased risk for depression in the FFI subgroup were predicted by permanent rural vs. urban residence, educational status, household income per person and stage of the andrological procedure.

The odds for significant distress and increased risk for depression in respondents with Mixed FI were predicted by educational status, duration of female's treatment and stage of the andrological procedure

The stage of the andrological procedure was the most significant predictor of clinically significant distress and risk for depression in the subgroups with the male, female and mixed factors of infertility.

The impact of occupation on respondents' distress and risk for depression was less evident than the effect of age, income, permanent residence or educational status.

Infertility staff should be provided evidence-based training programs to help them understand how age, residence or education may influence male infertility-related distress.

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Conflicts of Interest

The authors declare no conflicts of interest.

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