

TAILORING MALE INFERTILITY IN NORTH MACEDONIA, WHERE ARE WE NOW? A RETROSPECTIVE AND PREDICTIVE EPIDEMIOLOGICAL

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Abstract

This retrospective study investigates the incidence and prevalence of male infertility in North Macedonia by analyzing data from two regionally focused cohorts encompassing 1,857 men aged 19–50 years. The overall infertility prevalence was 14.7%, with regional differences—urban centers like Ohrid (18.2%) and Centar Župa (17.5%) had higher rates than rural areas such as Vevčani (9.1%) and Debar (10.4%). Infertile men were significantly older (mean age 29.8 ± 4.8 years) than fertile counterparts (26.4 ± 4.9 years; $p < 0.005$). Rates of infertility increased notably after age 35.

Semen abnormalities—particularly asthenozoospermia, oligozoospermia, teratozoospermia, and azoospermia—were frequently observed. Normozoospermia was present in just over half of participants. Infections, notably with *Escherichia coli* and *Staphylococcus aureus*, were significantly associated with abnormal sperm parameters, suggesting a strong infectious etiology. Other contributing factors included oxidative stress, smoking, alcohol use, and environmental exposures.

The findings underscore the complexity of male infertility and the need for standardized diagnostic protocols, public health interventions, early screening, and enhanced reproductive health services. Addressing these issues is vital to reduce the growing burden of male infertility in North Macedonia.

Keywords: Male infertility, semen analysis, reproductive epidemiology, North Macedonia, bacterial infection, oxidative stress, public health

Introduction

Male infertility, defined as the inability to achieve pregnancy after 12 months of regular, unprotected intercourse, represents a significant and growing public health concern globally. It is estimated that infertility affects 8–12% of couples worldwide, with male factors solely responsible for approximately 20–40% of cases and contributing to up to 50% of all infertility diagnoses (Zegers-Hochschild et al., 2009; Agarwal et al., 2015). In North Macedonia and the broader Balkan region, the true prevalence of male infertility remains poorly understood, due in part to underreporting, cultural stigmas, and a healthcare focus traditionally oriented toward female reproductive health (Zhaku et al., 2019; Kochubovski M et al., 2023).

Addressing male infertility is critical not only for the wellbeing of affected couples but also for broader demographic, psychological, and socioeconomic implications (Mumtaz Z et al., McDonald EE., 2004). Infertility is often accompanied by emotional distress, social exclusion, and financial burden, particularly in cultures where procreation is strongly linked to identity and social value (Ergin et al., 2018). Environmental, lifestyle, and infectious factors—such as pollution, smoking, and genitourinary infections—further complicate the epidemiology of male reproductive dysfunction (Kaltsas, 2023; Barzani M et al., 2014).

Recent regional data suggest that the burden of male infertility in North Macedonia may be substantially higher than traditionally assumed. According to findings from our research and the research in the doctoral thesis of Dr. Vegim Zhaku, the estimated prevalence of male infertility in the general population may reach as high as **46.95% \pm 4%**, based on combined semen abnormalities and regional modeling (Zhaku V., 2022). The data are consistent with

laboratory-based studies showing that between 44% and 50% of men evaluated for infertility present with at least one pathological semen parameter, including oligozoospermia, asthenozoospermia, teratozoospermia, or azoospermia (Beadini et al., 2016; Zhaku et al., 2019). Moreover, infections caused by organisms such as *Escherichia coli* and *Staphylococcus aureus* are commonly detected in infertile men with poor sperm quality, suggesting a strong infectious etiology in a significant number of cases (Das S et al., 2022; Agarwal A et al., 2018; Huang C et al., 2015). These findings highlight the need to adopt a comprehensive diagnostic framework that includes microbiological, hormonal, and oxidative stress assessments.

Despite the growing evidence, there is still a lack of consolidated national data to guide preventive or therapeutic approaches. As such, this study aims to bridge that gap by analyzing retrospective data from two regional cohorts, providing a clearer picture of the prevalence, patterns, and risk factors of male infertility in North Macedonia.

Materials and methods

This retrospective, descriptive study analyzed male infertility using data from two previously published studies conducted in North Macedonia. The analysis focused on clinical, hormonal, and microbiological parameters associated with infertility in the region.

Data sources and study population:

- **Beadini et al., 2014:** Data were collected from July 2012 to June 2013 at the biochemical laboratory “Albimedika” in Tetovo, the Clinical Hospital Tetovo, and the Scientific Research Laboratory of the Faculty of Medical Sciences, State University of Tetova. This cohort included 481 men aged 20–50 years from the Pollog region.
- **Zhaku et al., 2019:** Data were retrospectively collected from 1,368 semen analyses performed between 2014 and 2018 at the Daron Med laboratory, encompassing seven municipalities in southwestern North Macedonia (Kicevo, Ohrid, Debarca, Struga, Vevcani, Centar Zupa, and Debar). Ethical approval for this study was obtained from the institutional committee.

This retrospective study analyzed male infertility in North Macedonia using data from two previously published regional studies. The combined sample included men aged 19 to 50 years who had experienced infertility for at least one year and were referred by healthcare professionals for semen analysis. Patients with incomplete records or those not meeting these criteria were excluded.

Semen samples were collected and analyzed following World Health Organization (WHO) guidelines (2002 and 2010 editions). Key parameters assessed included semen volume, sperm concentration, motility, and morphology presented in the table below.

Table 1 Classification of participants based on the standard diagnostic thresholds.

Condition	Criteria
Normozoospermia	All parameters within normal range (per WHO 2002/2010)
Oligozoospermia	Sperm concentration < 20 million/mL (WHO 2002) or < 15 million/mL (WHO 2010)
Asthenozoospermia	< 50% progressive motility
Teratozoospermia	< 14% normal morphology by strict Kruger criteria
Oligoasthenoteratozoospermia (OAT)	Combined abnormalities in count, motility, and morphology
Azoospermia	Absence of sperm in ejaculate
Aspermia	Absence of ejaculate

Semen analyses were performed using manual counting with a Neubauer chamber and phase-contrast microscopy. For samples showing abnormal semen parameters, microbiological cultures were conducted to detect bacterial infections, primarily *Escherichia coli* and *Staphylococcus aureus*.

Statistical analysis included descriptive statistics, regression analysis, and calculation of prevalence rates, performed using SPSS and Microsoft Excel. Results were reported as means with standard deviations for continuous variables and percentages for categorical data.

Ethical approval was obtained for the retrospective use of anonymized laboratory data in accordance with institutional guidelines.

Results

A total of 1,857 men aged 19–50 years were included: 481 from the Pollog region and 1,368 from the southwestern municipalities. The mean age of infertile men was 29.8 ± 4.8 years, significantly higher than fertile men (26.4 ± 4.9 years; $p < 0.005$).

The overall prevalence of male infertility was 14.7%, with notable regional variation:

- Ohrid (18.2%),
- Centar Župa (17.5%)
- Debar (10.4%)
- Vevčani (9.1%),

Semen analysis findings:

- **Normozoospermia:** Observed in just over half of all subjects
- **Abnormalities:** Oligozoospermia, asthenozoospermia, and oligoasthenoteratozoospermia were the most frequent abnormalities among infertile men
- **Azoospermia:** Detected in a subset of patients

Association with bacterial infections:

Bacterial infections, particularly with *E. coli* and *S. aureus*, were strongly associated with abnormal semen parameters. The presence of these pathogens correlated with reduced sperm motility and increased rates of oligozoospermia and asthenozoospermia.

Risk factors:

Additional risk factors identified included advanced age, smoking, alcohol consumption, and possible environmental exposures. Oxidative stress was highlighted as a contributing mechanism for impaired sperm quality, especially in men with concurrent infections.

Summary tables

In the text below, we will try to elaborate all the data retrieved from this two major retrospective studies done in the western part of the country.

Table 2 presents the distribution of various semen abnormalities in a cohort of 486 men assessed for infertility in the Pollog region of North Macedonia. Normozoospermia was identified in 50.3% of the cases, indicating that more than half of the individuals had normal semen profiles according to WHO criteria. The most common abnormality was oligozoospermia (36.5%), defined by a sperm concentration below the normal threshold. Other conditions, including asthenozoospermia (reduced motility), teratozoospermia (abnormal morphology), and

azoospermia (absence of sperm), were also observed but with lower frequency. Hypospermia and aspermia were relatively rare. These findings highlight the heterogeneity of semen abnormalities among infertile men in this region.

Table 2: Distribution of spermogram types and patient counts (Beadini et al., 2016)

Types of spermogram	Percentage of patients (%)	Number of patients (n=486)	Description of spermogram
Normozoospermia	50.3%	241 patients	>20 million sperm cell/ml ejaculate
Oligozoospermia	36.5%	176 patients	<20 20 million sperm cell/ml ejaculate
Hypospermia	2.70%	11 patients	<2 ml amount of ejaculation
Asthenozoospermia	2.49%	12 patients	<50% of sperm cell motion
Teratozoospermia	2.07%	10 patients	<30% normal form of sperm
Azoospermia	6.44%	31 patients	Complete lack of sperm in the ejaculate
Aspermia	1.03%	5 patients	Lack of ejaculation

Table 3: Association between sperm abnormalities, bacterial infections, and motility (Beadini et al., 2016)

Types of spermogram	Number of patients (n=486)	Spermoculture gram-negative bacteria 70% <i>Escheria coli</i>	Spermoculture gram-positive bacteria 30% <i>staphilococcus aureus</i>	Percentage of Sperm mobility
Normozoospermia	241	/	/	75%-85%
Oligozoospermia	176	45 % E.c	25% S.a	30%
Azoospermia	31	25% E.c	45% S.a	0%
Asthenozoospermia	12	15% E.c	65% S.a	20%
Teratozoospermia	21	35% E.c	45% S.a	20%
Aspermia	5	/	/	/

This table above demonstrates the correlation between specific semen abnormalities and the presence of bacterial infections, specifically *Escherichia coli* (gram-negative) and *Staphylococcus aureus* (gram-positive), in a cohort of 486 patients. Notably, patients with oligozoospermia, azoospermia, and asthenozoospermia showed a high prevalence of bacterial colonization. Sperm motility was markedly reduced in these groups compared to normozoospermic individuals, suggesting a strong link between infection and impaired sperm function. In contrast, normozoospermic and aspermic patients showed no significant bacterial presence, indicating that infectious etiology is predominantly associated with abnormal sperm parameters.

Table 4: Regional prevalence and demographic breakdown, and the number of infertile male (Zhaku et al., 2019)

City	19 - 24	25-29	30-34	35-39	40-45	Total
Vevchani	80	86	78	106	105	455
	7	19	26	11	5	68
Debar	988	1004	973	886	758	4609
	13	41	63	29	15	161
Debarca	105	136	147	157	140	685
	8	20	31	9	4	72
Kicevo	2419	2577	2617	2465	2239	12317
	18	81	143	39	21	302
Ohrid	1632	1901	1981	1990	1740	9244
	16	117	194	52	19	398
Struga	2982	3419	3016	2578	2411	14406
	21	83	161	34	17	316
Centar Zhupa	357	365	345	310	314	1691
	3	12	26	7	3	51
Total	8563	3789	9157	8492	7707	43407
	86	373	644	181	84	1368

Table 4 summarizes the prevalence of male infertility across seven municipalities in southwestern North Macedonia. The total number of evaluated males aged 19–45 years is presented alongside the number of confirmed infertility cases and corresponding prevalence rates. Vevčani recorded the highest rate (14.9%), followed by Debarca (10.5%), while the lowest rates were observed in Kičevo (2.5%) and Debar (3.5%). The regional differences suggest potential influences of environmental, socioeconomic, or healthcare-related factors. These disparities underline the need for region-specific public health strategies and awareness campaigns to address male reproductive health.

In the table 5 we have analyzed and compared the mean age (\pm standard deviation) of fertile and infertile men across various municipalities. In all regions, infertile men were significantly older than their fertile counterparts, with $p < 0.0005$. The mean age of infertile men ranged from 29.0 years in Vevčani to 32.0 years in Debar, while fertile men were consistently younger, typically in their mid-to-late twenties. These findings confirm that advancing age is a statistically significant factor associated with male infertility in this population. The consistency of this trend across all regions strengthens the case for early reproductive evaluation and intervention.

Table 5: Infertility males diagnosed by age and municipality (Zhaku et al., 2019)

Table 3: Inherently males diagnosed by age and municipality (Zhaku et al., 2019)											
	City	Vevchan i	Deba r	Debarc a	Kicev o	Ohri d	Strug a	Centa r Zhup a	Overall		
	N	68	161	72	302	398	316	51	1368		
Males in the Study	Mean										
	(± SD)	26,78 ±	30,06 ±	27,68 ±	30.01 ±	30,22 ±	28,58 ±	29,63 ±	29,45 ±		
	age (years)	6,14	± 6,29	5,13	± 5,66	± 5,32	± 4,70	± 4,30	5,47		

	Media n (5- 95) age (years)	25,5 (19,45 – 40,65)	29 (21,1 – 42,9)	27 (20,65 – 39,7)	29 (22 – 41,85)	29 (23- 41,05)	28 (22- 39)	29 (23,55 – 40,8)	28 (22 – 41)
Fertile	N	44	100	45	165	195	195	20	764
	Mean (± SD) age (years)	25,57 ± 5,93	29,39 ± 6,39	26,42 ± 4,93	29,56 ± 5,40	29,92 ± 5,17	28,03 ± 4,76	28,55 ± 4,29	28,8 ± 5,44
	Media n (5- 95) age (years)	24 (19- 38,75)	28,5 (20,0 5 – 41,95)	26 (20- 3/-8,7)	29 (22- 41)	29 (22,8- 41)	27 (22- 39)	28 (23- 39,8)	28 (21- 40)
Infertile	N	24	61	27	137	203	121	31	604
	Mean (± SD) age (years)	29 ± 6	31,96 ± 6,01	29,78 ± 4,83	30,55 ± 5,94	30,51 ± 5,45	29,47 ± 4,48	30,32 ± 4,23	30,28 ± 5,39
	Media n (5- 95) age (years)	28 (21,25 – 44,25)	29 (24 – 43,9)	28 (24 – 41,6)	29 (22- 42)	29 (24- 42)	20 (24 – 39)	29 (25,6 – 42)	29 (24 – 42)
<i>p<0,0005 (age between cities differed significantly)</i>									

The last table details the distribution of different semen profile types across seven municipalities in southwestern North Macedonia. Normozoospermia (NZS) was most prevalent in all regions, particularly in Ohrid, Kičevo, and Struga. However, various abnormalities such as azoospermia (AS), oligozoospermia (OZS), oligoasthenozoospermia (OAZ), asthenozoospermia (AZS), and combinations such as oligoasthenoteratozoospermia (OAT) were also observed. Ohrid showed the highest number of cases with complex abnormalities like OAT, while Centar Župa, despite its smaller sample, had a relatively high proportion of pathological profiles. These results reflect a regional diversity in semen quality and underscore the importance of localized reproductive health assessments and interventions.

Table 6: Semen profile distribution by municipality (Zhaku et al., 2019)

City	NZS	AS	OZS	OAZ	AZS	OTZ	TZS	OAT	TOTAL
Vevchani	44	3	6	4	5	2	1	3	68
Debar	100	7	14	7	16	5	3	9	161
Debarca	45	2	5	7	4	2	2	5	72
Kichevo	165	13	28	33	27	8	9	19	302
Ohrid	195	18	36	44	53	12	11	29	398
Struga	195	10	23	29	28	6	8	17	316
Centar Župa	20	3	7	6	7	1	1	6	51
Total	764	56	119	130	140	36	35	88	1368

NZS – Normozoospermia, AS – Azoospermia, OZS- Oligozoospermia, OAZ - Oligoasthenozoospermia, AZS – Asthenozoospermia, OTZ – Oligoteratozoospermia, TZS – Teratozoospermia, OAT – Oligoasthenoteratozoospermia

Discussion and Conclusions

The findings of this study provide one of the most comprehensive epidemiological overviews to date regarding male infertility in North Macedonia, revealing important regional trends and biological correlates revealing a prevalence and pattern of semen abnormalities closely aligned with both regional and international literature. The data indicate that infertility rates rise significantly after the age of 35, highlighting the impact of advancing age on male reproductive potential. Approximately 44–50% of men evaluated for infertility were found to have abnormal semen parameters, such as reduced sperm count, motility, or morphology, which aligns with findings from both regional and international studies. In the south-western region, 44.2% of men had semen parameters below WHO-recommended thresholds, while in the western (Pollog) region, nearly half of the examined men also had pathological findings, confirming that male infertility is a significant public health issue in the country.

Comparing these findings with other regional and global studies, the observed rates are consistent with the global estimate that male factors contribute to approximately 50% of infertility cases (Schlegel PN., 2021). The most common semen abnormalities - oligozoospermia, asthenozoospermia, and oligoasthenoteratozoospermia - are also frequently reported worldwide, and a similar age-related increase in infertility is observed in both local and international data. Notably, environmental factors such as air pollution, which is especially problematic in the Western Balkans, are increasingly recognized as contributors to declining male fertility, with particulate matter and heavy metals negatively affecting sperm production and motility (Zhaku V et al., 2021). A considerable proportion of these cases with poor semen quality were linked to infectious causes, particularly bacterial infections like *Escherichia coli* and *Staphylococcus aureus*, underscoring the important role of infections in male infertility.

Differences between the two Macedonian regions studied may be attributed to several factors. Cultural attitudes that stigmatize male infertility or prioritize female evaluation can further delay diagnosis and intervention, a phenomenon noted both locally and in broader Balkan and global contexts. Socioeconomic status and access to healthcare may also contribute to regional disparities, as men in more developed areas or those with greater health awareness are more likely to seek diagnosis and treatment.

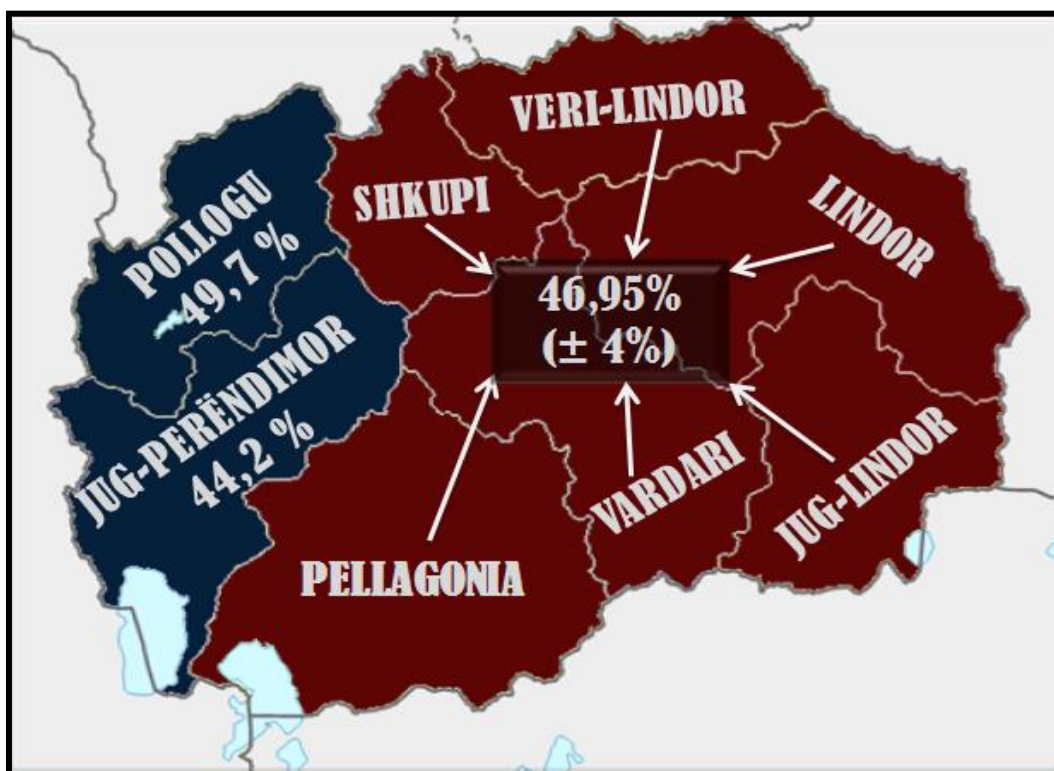


Figure 1 A visual representation of the estimated **prevalence of male infertility** across various statistical-planning regions in North Macedonia. Synthesized data derived from laboratory-based research, retrospective studies, and projections from the Dr. Vegim Zhaku doctoral thesis.

Male infertility in North Macedonia represents a substantial and under-addressed public health issue, with multifactorial origins encompassing biological, infectious, environmental, and sociocultural determinants. The observed prevalence of 14.7% in this study likely underestimates the true national burden, given referral biases and limited access to diagnostic services in rural areas. Drawing from broader population-level assessments, including findings from our doctoral thesis, the estimated national prevalence of male infertility may be as high as **46.95% ± 4%**. This figure is consistent with the proportion of men exhibiting suboptimal semen parameters in both the southwestern and northwestern regions of the country. Such a high estimated prevalence underscores the need for urgent action. The consistency of pathological semen findings across different municipalities and age groups reveals not only the biological and infectious dimensions of infertility but also signals gaps in awareness, screening, and access to care.

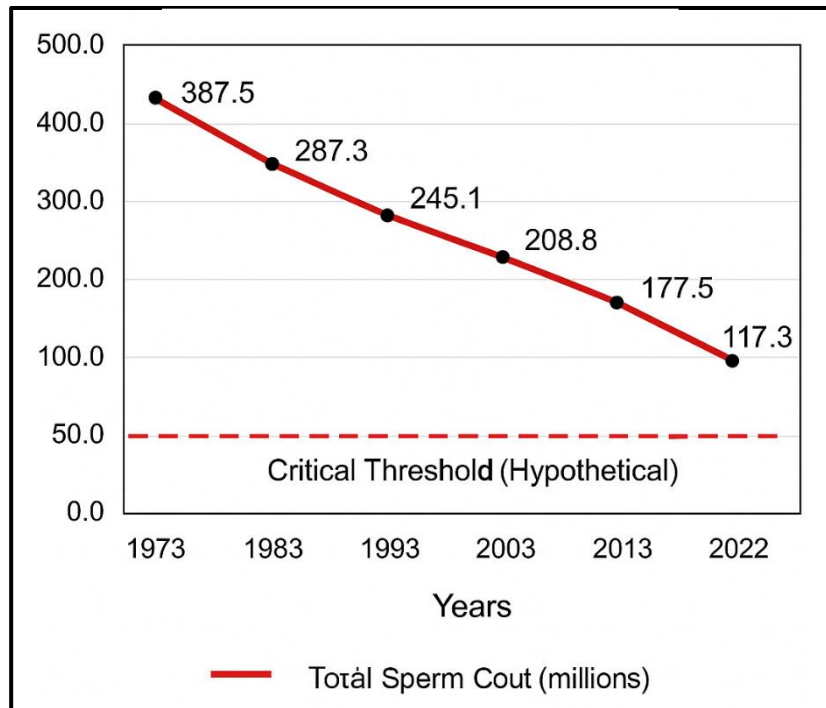


Figure 2 Decline in total sperm count over the last five decades

Male infertility is an emerging global health concern, often linked to declining sperm quality and count. Numerous studies have highlighted a steady and alarming decrease in sperm parameters over recent decades, so is the systematic review and meta-regression by Sengupta et al. and Levine et al. revealed a significant drop in total sperm count—from 337.5 million in 1973 to 137.5 million in 2013, representing a 59% decrease. Based on an estimated annual decline of -0.75% , by 2022 the count would be approximately 117.3 million (Zhaku V, 2022). If this trend continues, the implications for natural fertility, population dynamics, and public health systems may be profound. While this global issue has been widely acknowledged, this study is among the first to address it specifically within the context of North Macedonia and the Balkan region. Although no national data currently exist for total sperm count, the rising demand for private fertility services strongly suggests that this trend is affecting our population as well. These insights reinforce the importance of developing **standardized national infertility screening protocols**, improving **access to reproductive services**, and launching **education campaigns** aimed at destigmatizing male infertility and promoting early evaluation—particularly among men over the age of 30. The introduction of a national infertility registry and investment in prospective, multicenter research would help validate these estimates and guide precision public health strategies.

Despite its strengths, the study has several limitations. First, the retrospective nature of the data and reliance on laboratory referrals introduces potential selection bias, limiting generalizability. Second, there was no detailed assessment of occupational, dietary, or endocrine variables, which are known contributors to infertility. Third, the absence of longitudinal follow-up means that temporal changes in fertility status or outcomes of interventions were not captured. Moreover, psychological and sociocultural variables—such as stigma, stress, and gender-related biases in infertility care—were not evaluated, although they are highly relevant in the Balkan context (Ergin et al., 2018).

In conclusion, addressing male infertility in North Macedonia requires a multifaceted approach, including early diagnosis, public education, environmental improvements, and the creation of standardized protocols for evaluation and management. These actions are essential not only for

improving reproductive outcomes but also for reducing the psychosocial burden associated with infertility and supporting the country's demographic and public health objectives.

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