Diabetes mellitus. 2015;18(3):93-98

Диагностика и лечение ретроградной эякуляции как проявления урогенитальной формы автономной диабетической полинейропатии

Курбатов Д.Г., Галстян Г.Р., Роживанов Р.В., Лепетухин А.Е., Шварц Я.Г.

ФГБУ Эндокринологический научный центр, Москва
(директор – академик РАН И.И. Дедов)

Актуальность проблемы ретроградной эякуляции (РЭ) заключается в развитии экскреторного бесплодия у молодых пациентов с сахарным диабетом 1 типа (СД1) в сочетании с выраженным психологическим дискомфортом, что дополнительно снижает качество жизни.

Цель. *Оптимизация диагностики и методов лечения РЭ, обусловленной урогенитальной формой автономной диабетической нейропатии у больных СД1.*

Материалы и методы. *В исследование были включены 30 пациентов с СД1 с абсолютной РЭ. Возраст 32 [30; 35] года. Длительность СД составила 17 [12; 22] лет. Гликированный гемоглобин HbA_{1c} 7,4% [6,9; 8,0]. У всех пациентов на момент включения в исследование в посторгазменной моче определялись сперматозоиды в большом количестве. Всем пациентам выполнена трансуретральная ирригационная уретроскопия, при которой определялось несмыкание шейки мочевого пузыря. Затем под слизистую оболочку задней уретры через специальную инъекционную иглу введен объемообразующий, биоинертный, биосовместимый материал, до момента смыкания противоположных краев уретры. Контрольный анализ эякулята проведен через 1 неделю после операции.*

Результаты. *Восстановление антеградной эмиссии спермы достигнуто у 22 (73%) пациентов. Длительность сохранения эффекта от хирургического лечения составила 7 [2; 12] мес. У 27% пациентов с антеградной эякуляцией (6 человек) длительность сохранения эффекта составляла 1 год и более (до 2 лет у одного пациента). У партнерш 4 пациентов (13% от выборки) наступило спонтанное зачатие, у 3 из них (10% от выборки) беременность закончилась родами здоровых детей, а у одного – естественным прерыванием беременности в сроке 8 недель по неустановленной причине.*

Выводы. *Применение данного метода лечения обеспечивает эффективное восстановление физиологического пассажа эякулята по мочеиспускательному каналу. Операция малотравматична за счет выполнения через естественные мочевыводящие пути, не приводит к нарушению оттока мочи из мочевого пузыря и не требует установки уретрального катетера. Срок госпитализации не более 4 дней. Во всех случаях получен естественный эякулят для программ искусственного оплодотворения.*

Ключевые слова*: ретроградная эякуляция; автономная нейропатия; анэякуляция; экскреторное бесплодие*

Diagnostic and treatment of retrograde ejaculation as a manifestation of urogenital form of autonomic diabetic polyneuropathy

Kurbatov D.G., Galstyan G.R., Rozhivanov R.V., Lepetukhin A.E., Shwarts Y.G.
Endocrinology Research Centre, Moscow, Russian Federation

Background. *Retrograde ejaculation in patients with type 1 diabetes mellitus is a complication of autonomic neuropathy that causes excretory infertility. It can be partial (reduction of ejaculate) or total (absence of ejaculate) and occurs in 10%–20% of men with type 1 diabetes mellitus.*

Aim. *The aim of the study was to assess the effectiveness of a new endoscopic method for retrograde ejaculation correction and antegrade ejaculation restoration.*

Materials and methods. *We included 30 patients with type 1 diabetes mellitus who had spermatozoa present in their post-orgasmic urine and ultrasonographic evidence of impaired or absent bladder neck closure. The mean age of participants was 32 (30–35) years, mean duration of diabetes was 17 (12–22) years and mean preoperative glycated haemoglobin level was 7.4% (6.9%–8.0%). All participants had total retrograde ejaculation. We used conventional irrigated urethrocystoscopy under local anaesthesia. During urethroscopy, bladder neck gaping was observed in all cases. Biocompatible material was injected at three points under the mucous layer of the posterior urethra, reaching the closing of the opposite edges of the urethra. A spermiogram was examined 1 week after the operation.*

Results. *Restoration of antegrade ejaculation was achieved for 22 patients (73%), and the effects persisted for a mean of 7 (2–12) months. The spouses of four men became pregnant after surgery. In one case, the pregnancy resulted in a spontaneous abortion at gestational week 8, but the other three cases continued normally.*

Diabetes mellitus. 2015;18(3):93-98

Conclusion. *This new method provides a highly effective means of restoring the physiological passage of the ejaculate. The operation is a low-invasive endoscopic procedure that does not disrupt urination, and it is possible to receive ejaculate of sufficient.*
Key words: *retrograde ejaculation; autonomic neuropathy; anejaculation; excretory infertility*

DOI: 10.14341/DM2015393-98

Diabetes mellitus (DM) is a systemic disease characterised by the potential for the development of specific lesions of various organs and body systems, including genitourinary systems. Diabetic neuropathy is one of the most frequent complications of DM. Diabetes may be considered as the only cause of damage to the peripheral nervous system when all other causes, such as toxic (alcohol) damage, endocrine diseases (hypothyroidism), multiple sclerosis and others, have been excluded [1].

The incidence of various forms of diabetic neuropathy in patients with diabetes ranges from 65% to 80%. The second highest frequency of occurrence, after diffuse diabetic polyneuropathy, is autonomic diabetic neuropathy (ADN). ADN is diagnosed in 15% of patients at the time of diabetes diagnosis and in 50% of patients 15–20 years from the onset of the main disease [1].

The main cause of urogenital disorders in DM is ADN, which is a specific diabetic complication that involves the parasympathetic and sympathetic nervous systems of urinary organs [1-4].

There are 3 forms of clinical manifestations of urogenital ADN: diabetic cystopathy (problems with bladder emptying and bladder atony), erectile dysfunction (ED) and retrograde ejaculation (RE) [5, 6]. RE, as a complication of diabetes, is found in 15%–18% of cases and primarily in patients with type 1 diabetes mellitus (DM1) [2]. The incidence of and has been reported to range from 10% to 20% [4].

RE is a disruption of the process of ejaculation, where the ejaculate is redirected into the bladder [3, 6]. RE may be partial (partial decrease in the ejaculate volume) or absolute, where the full volume of the ejaculate is thrown into the bladder as a result of lowering of the tonus of its neck muscle [3].

RE is considered an important condition requiring urgency treatment because of development of excretory infertility in young patients with DM1. In addition, the lack of physiological ejaculation results in significant psychological discomfort, which further reduces the quality of life. Known conservative and surgical treatments of RE are ineffective, involve serious side effects, are limited in patients with diabetes and often present a purely historical interest.

Currently, the method of obtaining sperms from post-ejaculation urine for the purpose of subsequent use in assisted reproductive technology (ART) has drawbacks, the main being the low quality of the sperms.

Puncture of the testis or epididymis is an invasive procedure that carries a risk of postoperative complications. These are particularly undesirable for patients with diabetes and often yield an unsuitable material (immature sperms) for use in assisted reproduction programs [6].

According to the literature, in 1998, the first 2 attempts were made to correct RE via the injection of collagen into the bladder neck in patients with good results; however, this technology has not received further development and application [7]. Given the urgency and seriousness of RE and the lack of highly effective and safe treatments, we made the attempt to optimise the diagnosis and treatment of RE due to urogenital ADN in patients with DM1.

Aim

The goal is optimisation of the diagnosis and treatment of RE due to urogenital ADN in patients with DM1.

Materials and methods

A prospective cohort study was conducted to assess the efficacy and safety of a new surgical treatment method for RE in patients with DM1. The study included 30 patients who had undergone clinical examination at the offices of the Department of Conservative and Surgical Methods for the Treatment of Diabetic Foot (Department Head Prof. Galstyan G.R., MD PhD) and Department of Andrology and Urology (Department Head Prof. Kurbatov D.G., MD PhD), Endocrinology Research Center (ERC), Ministry of Health, Russian Federation, between 2012 and 2015. The study protocol was approved at the meeting of the Academic Council of the ERC, no. 4 2012 and the local ethics committee of the Endocrinology Research Center, Ministry of Health, Russian Federation (minutes of the review no. 2 date 05.02.2013).

Criteria for inclusion:

1. Presence of DM1
2. Male gender
3. Heterosexual
4. Legally adult
5. Presence of sexual partners and sexual attempts
6. Urogenital form of diabetic neuropathy

Exclusion criteria:

1. Incompetent/incapacitated subjects

Diabetes mellitus. 2015;18(3):93-98

2. Suspicion of serious mental illness, drug addiction or alcoholism according to the medical history and/or clinical examination
3. A history of trauma or surgery of the genitals
4. Hypogonadism, hypothyroidism, hyperprolactinemia, hypercortisolism
5. Vasculogenic form of ED

All patients included in the study underwent diagnostic testing, followed by surgery.

All patients signed an informed consent form to participate in the study.

Preoperative physical examination included sperm analysis in the post-ejaculation urine; ultrasound of the genitourinary system and electromyographic study to determine the speed of the pudendal nerve impulse, for which Nicolet Viking IV P unit was used (Nicolet Biomedical, USA).

Endoscopic surgical correction of RE was achieved by injection of bulking material under the mucous membrane of the bladder neck, followed by evaluation of the effectiveness of the surgical treatment. The essence of the surgical treatment of RE is endoscopic injection of a collagen-based bulking material under the mucous membrane of the posterior urethra and bladder neck. This material is approved for use in the Russian Federation and is widely used in endourology. The aim is to eliminate the aperture in the bladder neck during ejaculation, which provides recovery of the physiological passage of the ejaculate through the urethra in the ejection phase.

All 30 patients, with an average age of 32 (30; 35) years, were initially diagnosed with absolute RE. Of these patients, 29 men had no children of their own; 1 had a 7-year-old child. The average duration of the current DM1 diagnosis was 17 years (12; 22) years. All patients underwent preoperative correction of glycaemic levels through individual training and optimisation of insulin therapy. At the time of surgery, the median glycated haemoglobin (HbA1c) in the observation group was 7.4% (6.9; 8.0).

All 30 patients received endoscopic injection of the bulking material. During surgery, dilation of the bladder neck was visualised with the use of irrigation ureteroscopy. Collagen was injected under the mucous membrane of the bladder neck through a special needle (needle length: 32 cm, diameter: 0.8/1.6 mm; length of the distal end: 7 mm), sequentially in 3–5 points at 14, 18 and 22 h of the conditional dial, to a depth of 3–5 mm. As the bulking material was being injected, bulging (protrusion) of the mucous membrane of the opposite edges of the urethra was clearly visible. This effect was tentatively designated as 'cheeks effect'. The average duration of surgery was 17 ± 8 min. The volume of collagen administered was 9 ± 4 ml, depending on the size of the original aperture. No complications, such as urethritis, acute urinary retention, bleeding or difficulty in urination, were observed in any patient. Postoperative ultrasound demonstrated closure of the bladder neck edges in all men.

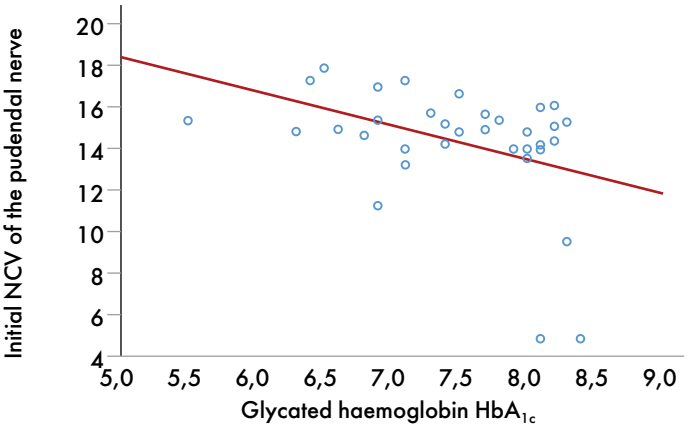

Figure 1. Correlation between HbA1c (%) and nerve conduction velocity (NCV) of the pudendal nerve (r = –0.41; p = 0.012)

Control semen analysis was performed for all patients a week after surgery.

Statistical data was processed using the application package Statistica (StatSoft Inc. USA, version 6.0).

Results

The intensity of manifestations of urogenital neuropathy in patients was independent of age, BMI and duration of diabetes but depended on the level of compensation of carbohydrate metabolism. There was a statistically significant moderately negative correlation between HbA1c levels and urogenital symptoms of neuropathy (Fig. 1).

According to an electromyographic test, the nerve conduction velocity (NCV) of the pudendal nerve was below the normal values. Notably, there was a reduction in the M-response amplitude, increase in the residual latency and high threshold of the M-response, which are characteristic features of the axonal/demyelinating process, the basis of diabetic polyneuropathy. The results of the electromyographic tests of the pudendal nerve are presented in the Table 1.

The surgical treatment (endoscopic correction of the RE by introduction of the bulking material under the mucous membrane of the bladder neck) was effective (appearance of antegrade ejaculation) in 73% (22 of 30) patients. The patients' characteristics ac-

Table 1

Electromyography results of pudendal nerve stimulation in patients with DM1

Parameters	Test results (M+/–), p > 0.05	Normal range
M-response amplitude	0.89 ± 0.17	>3.5
NCV, m/s	14.2 ± 2.5	>19.7
Residual latency, ms	7.6 ± 1.6	<3.0
Excitability threshold, mA	80 ± 17	<20

Diabetes mellitus. 2015;18(3):93-98

Table 2

Patients' characteristics according to surgical treatment outcomes

Parameter	Positive outcome	Negative outcome	p
Age, years	33 (30; 39)	30 (29; 32)	0.11
BMI, kg/m^2	26.1 (24.5; 27.1)	24.1 (23.7; 25.9)	0.12
DM1 duration, years	15 (10; 21)	21 (16; 23)	0.04
HbA_{1c}, %	7.1 (6.8; 7.7)	7.8 (7.5; 8.0)	0.04

Table 3

Results of semen analysis of patients with restored antegrade ejaculation

Parameter	Value
Ejaculate volume, ml	0.9 (0.5; 1.5)
Sperm count, 106/ml	65 (32; 113)
Sperm motility A+B, %	17 (14; 37)
Morphologically normal,%	20 (11; 35)

cording to the outcomes of the surgical treatment are shown in Table. 2.

Compared with patients with restored antegrade ejaculation, those who showed no effect of the surgical treatment had significantly worse indicators of carbohydrate metabolism compensation as well as longer diabetes duration. All patients who showed no effect of surgery were given recommendations on managing the underlying disorder. In addition, the patients were provided with information on infertility treatment through the use of ART.

The results of semen analysis of patients with restored antegrade ejaculation are presented in Table. 3.

Despite the fact that the volume of the ejaculate in the majority of patients did not reach the normal range (normal ejaculate volume was observed in only 1 patient), its quality was satisfactory (Fig. 2).

Only 2 patients (9% of patients with antegrade ejaculation) had oligoteratozoospermia and 1 patient had teratozoospermia accompanied by a normal sperm count. Asthenozoospermia was present in 83% of patients with antegrade ejaculation, but critical reduction in sperm motility with the lack of active motile forms was observed in only 2 patients. The duration of the surgery effect was 7 (2; 12) months, which made spontaneous conception possible. In 27% of patients with antegrade ejaculation (6 people), the duration of the surgery effect was ≥1 year (up to 2 years in 1 patient).

Out of 22 patients with a positive surgery effect (73% of the sample), 15 men (50% of the sample) had no reproductive plans during the study period, and the ejaculate was frozen for cryopreservation.

In 3 patients (10% of the sample) who planned conception, the quality of the ejaculate did not allow us to rely on a spontaneous result [The ejaculate volume was 0.3 (0.2; 0.6). The number of sperms in 1 ml of the ejaculate was 113 (5; 180) million, morphologically normal forms: 25% (1; 41), A + B mobility:

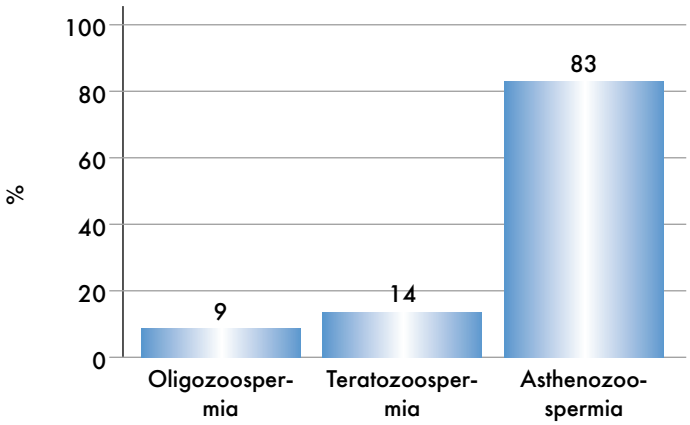

Рис. 2. Распространенность нарушений сперматогенеза.

22% (14; 40)]. These patients were encouraged to use ARTs and were included in the in vitro fertilisation program.

The female partners of 4 patients (13% of the sample) had spontaneous conception; 3 of them delivered healthy children and 1 had a miscarriage at 8 weeks of gestation for unknown reasons.

The results of semen analysis of the patients with spontaneous conception demonstrated mild-to-severe asthenozoospermia (Table 4).

The surgical treatment was effective in the following respects: antegrade ejaculation was achieved in 73% of cases, spontaneous conception in 13% of cases and birth of healthy offspring in 10% of cases. The treatment was safe, there were no postoperative complications in the patients, the recovery period was short (less than 4 days) and none of the patients withdrew from the study.

Discussion

The main goal of RE treatment is to restore the physiological passage of the ejaculate. The application of conservative and surgical methods of treatment is aimed at improving the tonus of the bladder neck muscle, which prevents the retrograde throw of the semen into the bladder. With conservative treatment, this could be achieved by stimulating the activity of the sympathetic nervous system or by blocking the effects of the parasympathetic system, as indicated by studies in 1974–1979 by different groups of scientists.`

Table 4

Results of semen analysis

Parameter	Value	Lower reference limit, WHO (2010)
Volume of the ejaculate, ml	1.2 (0.9; 1.6)	≥1.5
Sperm count, 106/ml	35 (27; 65)	≥15
Motility, A+B, %	29 (18; 39)	≥40%
Sperm morphology (normal forms, %)	18 (13; 20)	≥4%

Conservative treatment of RE may include the use antihistamines (brompheniramine), tricyclic antidepressants (imipramine) and other drugs, including anticholinergic and adrenergic agents [8-11]. Afara and El Tabie (2008) in their study obtained data on the efficacy of restoring antegrade ejaculation: imipramine was effective in 38% cases, ephedrine in 48% cases and the combinations of both drugs in 61.5% cases of RE due to diabetes. However, given the wide range of side effects of the above drugs, their use is limited in patients with diabetes because of the presence of various complications of the underlying disease [12].

The electroejaculation procedure is mainly used in patients with spinal cord injuries and after retroperitoneal lymph node dissection [14, 15, 16].

Currently, a technique of obtaining sperms from the urine for the purpose of use in various programs of ART is widely used. The limitation of this method is the low quality of the material. In a systematic review of the literature, Jefferys et al. (2012) reported a pregnancy rate of 13% using this method [17].

In recent years, the use of different surgical methods for obtaining sperms directly from the testes (MESA, PESA, TESE and TESA) has increased [18]. Sperms obtained using these methods may be used for intracytoplasmic sperm injection (ICSI). However, given the invasiveness of these procedures, their use is undesirable in patients with diabetes because of the risk of postoperative complications.

Given our results, as well as all the results of previous studies discussed above, we consider that our new method of treatment for RE in patients with DM1 is encouraging and promising, showing potential for providing satisfactory quantity and quality of semen for use in ARTs.

The method may be described as highly effective because the surgery is performed through the natural urinary tract and requires a minimum period of recuperation. Further research in this area with a greater number of patients will allow more detailed investigation of the problem and lead to the development of a new surgical treatment method for RE in patients with DM1.

Conclusions

A new method of endoscopic correction of ejaculation provides effective restoration of the physiological passage of semen through the urethra. The operation is non-invasive because it is performed through the natural urinary tract, does not lead to disruptions of the urine outflow from the bladder and does not require installation of a urethral catheter, which minimises the risk of complications. This surgery does not require long anaesthesia, and the duration of hospitalisation is 3–4 days. This method allows obtaining an ejaculate of satisfactory quality, which increases the chances of physiological conception and the use of the material for ARTs (if necessary).

Funding information and conflicts of interest

The authors declare no conflict of interest in writing this article.

The authors did not receive any fees for their work.

Список литературы

1. Эндокринология: национальное руководство. / Под редакцией Дедова И.И., Мельниченко Г.А. – М.: ГЭОТАР-Медиа; 2009. [*Endocrinology: national guidelines*. Ed by Dedov I.I., Mel'nichenko G.A. Moscow: GEOTAR-Media; 2009. (In Russ).]
2. Vinik AI, Maser RE, Mitchell BD, et al. Diabetic autonomic neuropathy. *Diabetes Care*. 2003;26(5):1553-1579. doi: 10.2337/diacare.26.5.1553
3. Дедов И.И., Роживанов Р.В., Курбатов Д.Г., и др. Особенности заболеваний мочеполовой системы при сахарном диабете. // Урология. – 2009. – №4 – С. 74-78. [Dedov II, Rozhivanov RV, Kurbatov DG, et al. Features of diseases of the genitourinary system in diabetes mellitus. *Urologiia* 2009;(4):74-78. (In Russ).]
4. Роживанов Р.В., Сунцов Ю.И. Эректильная дисфункция у больных диабетом в Российской Федерации. // Трудный пациент. – 2005. – Т. 3. – №9 – С.31-35. [Rozhivanov RV, Suncov JI. Erectile dysfunction in diabetic patients in the Russian Federation. *Trudnyj pacient*. 2005;3(9):31-35. (In Russ).]
5. Роживанов Р.В., Дубский С.А., Курбатов Д.Г., и др. Особенности заболеваний мочеполовой системы при сахарном диабете. // Сахарный диабет. – 2009. – Т. 12. – №2 – С.40-45. [Rozhivanov RV, Akimova AN, Dubsky SA, et al. Specific features of urogenital disorders in patents with diabetes mellitus. *Diabetes mellitus*. 2009;12(2):40-45. (In Russ)] doi: 10.14341/2072-0351-5396
6. Hampel C, Gillitzer R, Pahernik S, et al. Diabetes mellitus and bladder function. What should be considered? *Urologe A*. 2003;42(12):1556-1563. doi: 10.1007/s00120-003-0456-7
7. Lipshultz LI, Thomas AJ, Khera M. Surgical management of male infertility. In: *Campbell-Walsh Urology*, 9th ed. Philadelphia: «Saunders Elsevier»; 2007.
8. Comhaire F, Vermeulen A. Varicocele sterility: Cortisol and catecholamines. *Fertil Steril*. 1974;25(1):88-95.
9. Jonas D, Linzbach P, Weber W. The use of Midodrin in the treatment of ejaculation disorders following retroperitoneal lymphadenectomy. *Eur Urol*. 1979;5(3):184-187.
10. Stewart BH, Bergant JA. Correction of retrograde ejaculation by sympathomimetic medication: Preliminary report. *Fertil Steril*. 1974;25(12):1073-1074. doi: 10.1111/j.1439-0272.1978.tb03053.x
11. Stockamp K, Schreiter F, Altwein JE. Alpha-adrenergic drugs in retrograde ejaculation. *Fertil Steril*. 1974;25(9):817–820. doi: 10.1159/000279920
12. Arafa M, El Tabie O. Medical treatment of retrograde ejaculation in diabetic patients: a hope for spontaneous pregnancy. *J Sex Med*. 2008;5(1):194-198. doi: 10.1111/j.1743-6109.2007.00456.x
13. Reynolds JC, McCall A, Kim ED, et al. Bladder neck collagen injection restores antegrade ejaculation after bladder neck surgery. *J Urol*. 1998;159(4):1303. doi: 10.1016/S0022-5347(01)63592-4
14. Kamischke A, Nieschlag E. Update on the medical treatment of ejaculatory disorders. *Int J Androl*. 2002;25(6):333-344. doi: 10.1046/j.1365-2605.2002.00379.x
15. Brackett NL, Lynne CM, Ibrahim E, et al. Treatment of infertility in men with spinal cord injury. *Nat Rev Urol*. 2010;7(3):162-172. doi: 10.1038/nrurol.2010.7
16. Hsiao W, Deveci S, Mulhall JP. Outcomes of the management of post-chemotherapy retroperitoneal lymph node-associated anejaculation. *BJU Int*. 2012;110(8):1196-1200. doi: 10.1111/j.1464-410X.2011.10852.x
17. Jefferys A, Siassakos D, Wardle P. The management of retrograde ejaculation: a systematic review and update. *Fertil Steril*. 2012;97(2):306-312. doi:10.1016/j.fertnstert.2011.11.019

Diabetes mellitus. 2015;18(3):93-98

18. Choy JT, Ellsworth P. Overview of current approaches to the evaluation and management of male infertility. *Urol Nurs*. 2012;32(6):286-294, 304 quiz 295.

Kurbatov Dmitry Gennadyevich	MD, PhD, Professor, Head of Department of Andrology and Urology, Endocrinology Research Centre, Moscow, Russian Federation
Galstyan Gagik Radikovich	MD, PhD, Professor, Head of Department of Diabetic Foot, Endocrinology Research Centre, Moscow, Russian Federation
Rozhivanov Roman Viktorovich	MD, PhD, Senior research associate, Head of Department of Andrology and Urology, Endocrinology Research Centre, Moscow, Russian Federation
Lepetukhin Aleksander Evgenyevich	MD, PhD, Urologist, Department of Andrology and Urology, Endocrinology Research Centre, Moscow, Russian Federation
Shwarts Yana Grigoryevna	MD, Research fellow, Department of Andrology and Urology, Endocrinology Research Centre, Moscow, Russian Federation **E-mail: dr.shwarts@mail.ru**