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Global Secular Trend of Gonadal Size in Men: Review and Analysis of Publications

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Introduction. Notwithstanding the general increase in world population, there is a steady decline in birth rate. Studies have shown a tendency towards worsening of qualitative and quantitative indices of the ejaculate. From the foregoing we may also presume a decline in size of male gonads. Nevertheless, information about the tendency of change in testicular size in the population is currently unavailable.

Purpose of the study. Assessment of global secular trend as regards changes in the size of testes in men.

Materials and methods. A search was conducted on published scientific research in the English language and Russian language in Pubmed and eLibrary. Additional searches in citations of identifiable investigations. A selection of data from publications with metric characteristics of gonads in relatively healthy men aged 18–60 years. The mean of values obtained were determined and homogenized with the aid of formulae for volume calculations. Statistical analysis of the data was carried out with the aid of the program STATISTICA for Windows v.10.

Results. The search yielded 126 identified publications, published between 1902 and 2018. Analysis of the various works led to a selection of 33, which contained information that satisfied the inclusion criteria. Analysis of the obtained data did not reveal any trends in change of testicular size over the past century. Mean arithmetic weighted value was $17,43 \pm 5,64$; 95% CI (17,32; 17,54).

Conclusion. In the light of global trends towards a reduction in fertility, it is necessary to conduct a wide range of varied investigations in order to understand the nature of this process. Standardization of methods of assessment results obtained will help in reducing errors whilst assisting in the analysis of existing tendencies.

Key words: testicular size; testicular volume; orchidometry; secular trends

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Мировой секулярный тренд размера наружных половых желез у мужчин: обзор и анализ литературы

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Введение. Несмотря на общее увеличение народонаселения, за последние десятилетия отмечается устойчивая мировая тенденция к снижению рождаемости. Исследованиями доказана тенденция к ухудшению качественных и количественных показателей эякулята. Из этого можно предположить также наличие отрицательной динамики в изменении размера мужских половых желез. Тем не менее, информация о тенденциях в изменении размеров яичек в популяции отсутствует.

Цель исследования. Оценка мирового секулярного тренда в аспекте изменения размеров яичек у мужчин.

Материалы и методы. Поиск научных работ на английском и русском языках, оценивающих размер яичек, в Pubmed и eLibrary. Дополнительный поиск в цитируемой литературе идентифицированных исследований. Отбор данных из публикаций с метрическими характеристиками наружных половых желез у относительно здоровых мужчин 18–60 лет. Полученные данные усреднены и гомогенизированы с использованием формул вычисления объема. Статистическая обработка материала производилась с помощью программы STATISTICA for Windows v.10

Результаты. По результатам поиска идентифицировано 126 работы, опубликованные в период с 1902 по 2018 годы. Анализ публикаций привёл к селекции 33 из них, в которых содержащаяся информация соответствовала заданным критериям. Анализ полученных данных статистически значимых тенденций в изменении объёма яичка за последнее столетие не выявил. Среднее арифметическое взвешенное значение составило $17,43 \pm 5,64$; 95% ДИ (17,32; 17,54).

Заключение. В свете мировых трендов к снижению fertильности необходимо проведение большего количества различных исследований для понимания природы данного процесса. Стандартизация методов оценки их результатов позволит снизить погрешности и поможет в анализе существующих тенденций.

Ключевые слова: размер яичек; объём яичек; орхидометрия; секулярные тренды

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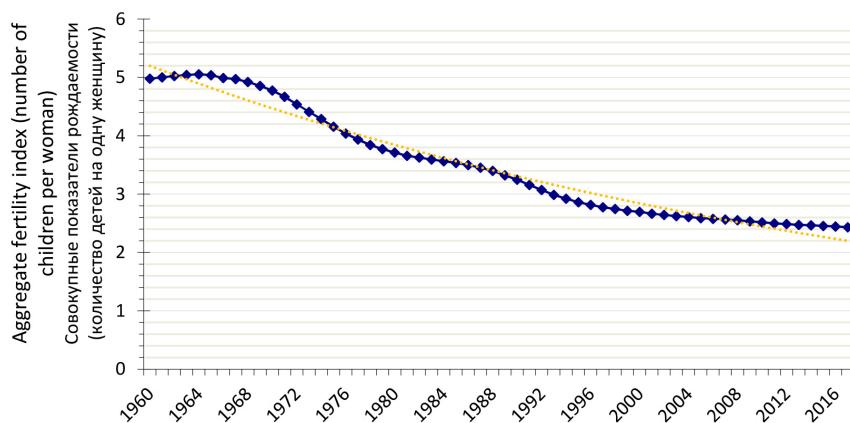
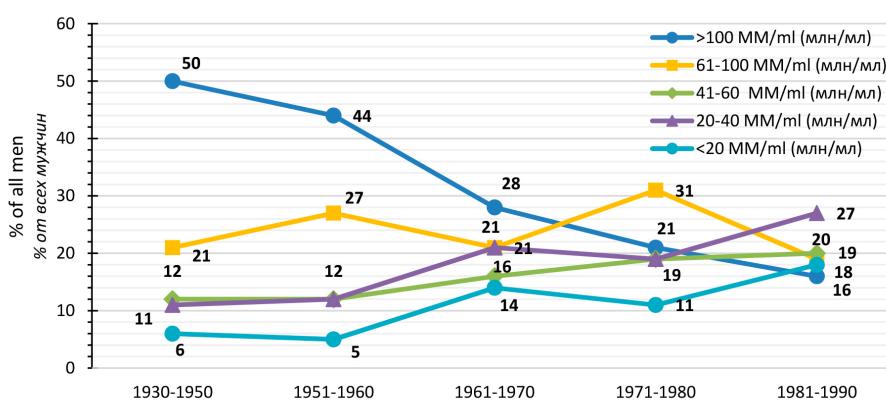
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Introduction

Reproductive health is one of the goals for the development humankind adopted by the General Assembly of the UN in 1994. Despite general increase in the population of the world, there has been a steady decline in fertility in the last decades [1, 2] (Figure 1). It must be noted that this problem is linked to the increase in several infertile couples worldwide.

Most research studies indicate that 15% of couples remain infertile after 1 year of attempting to conceive a child [4–6]. This information is based on the WHO report published in 1991 [7], as well as a row of other studies carried out over two past decades [8, 9]. Considering the global tendency towards a reduction in fertility, it is possible that currently, the percentage of couples without children is

higher than recognized above. Concerning gender, the male factor of infertility accounts for a little over 50% [10]. The ability of a man to impregnate a woman is closely related to the qualitative and quantitative characteristics of the ejaculate. Currently, the WHO has established a lower level of normal sperm concentration to $15 * 10^6 / ml$ [11]. Nonetheless, many authors concede that for normal fertility this parameter should be $40 * 10^6 / ml$ or higher [12–14]. The majority of studies in the first half of the 20th Century noted a rather high concentration of spermatozoa in the ejaculate of healthy men. On the average, this was about $100 * 10^6 / ml$ [15, 16]. In 1992, results of a meta-analysis were published for semen analysis of healthy men. The authors included the period from the 1930s to the 1990s of the previous century. From the results of the above, it was established that there is a global tendency towards

**Figure 1.** Aggregate indices of fertility (number of births per woman) worldwide, 1960–2017 years [3]**Рисунок 1.** Совокупные показатели рождаемости (число рождений на одну женщину) во всем мире, 1960–2017 годы [3]**Figure 2.** Percentage proportion of men with different ranges of sperm concentration in different periods of investigations (data from 27 publications). From Carlsen et al., 1992 [16]**Рисунок 2.** Процентное соотношение мужчин с различными диапазонами концентрации сперматозоидов в разные годы исследований (данные из 27 публикаций). Из Carlsen с соавт., 1992 [16]

the worsening of sperm quality (Figure 2) [16]. The initial results appeared doubtful, but after scrutiny and verification and taking into account geographical considerations among others, the results were found to be comparable. The observed reduction in the concentration of sperm of men in North America is about 1.5% per year and in Europe about 3.1% [17, 18]. According to data from contemporary population series, the sperm concentration in healthy men varies according to a geographical location but on the average ranges between $41\text{--}63 \times 10^6/\text{ml}$ [19–23].

It is important to note that the concentration of spermatozoa in the ejaculate is directly related to the size of the testis [24–28]. From the above information, one may propose the presence of a negative dynamic in testicular size. However, information about the trends in change of testicular size in the population is absent. The non-uniformity

of methods for measurement of testicular volume [29] and lack of standardization in the latter process leads to a wide variation of current data, thereby making retrospective analysis of the given parameter rather difficult.

Purpose of the study. The objectives of the current study are to evaluate the global secular trend in the change in the size of testes in men.

Materials and methods

We searched for studies in English and Russian languages that assessed testicular size. For this purpose, we employed resources from Pubmed and eLibrary. Also, we analyzed citations from the literature obtained, with subsequent inclusion of the same in the selection after satisfying the given criteria. We did not set limits about the date of

publication. From this volume of information, we selected data related to testicular size in men aged between 18–60 years. We excluded studies whose subjects were selected based on fertility or the presence of disease conditions such as varicoceles or cryptorchidism, that have the potential to affect testicular volume. From cadaveric studies, we excluded those that assessed volume or weight without removal of the epididymis or those which had no information about the extent of dissection of the specimens. Apart from that, in our review, we did not include studies in which only one linear dimension of the testis was measured, as well as those that employed Hynie orchidometer [30]. The next stage involved the homogenization of the various methods of measurement and calculation of the mean volume, the closest to the actual values.

For this purpose, we used the following formulae for the determination of the volume (V):

$$(1) V=m/1.038$$

where m — a mass of the organ; 1.038 — density.

$$(2) V=a*b*c*0.71$$

where a, b, c — corresponding length, width and height; 0.71 — Lambert's coefficient.

$$(3) V=a*b^2*0.71$$

where a, b — corresponding length and width; 0.71 — Lambert's coefficient.

$$(4) V=V_1/0.52*0.71$$

where V_1 — volume calculated using the ellipsoid or prolate spheroid formula; 0.52 — coefficient for ellipsoid or prolate spheroid formula; 0.71 — Lambert's coefficient.

$$(5) V=a*b^2*0.39$$

where a, b — corresponding length and width, calculated by means of external measurements without taking skin into the account; 0.39 — correction coefficient.

$$(6) V=VPr*0.816$$

where VPr — volume obtained with the aid of Prader orchidometer or similar meter; 0.816 — correction coefficient.

$$(7) V=VTh/0.52*0.39$$

where VTh — volume obtained with the aid of Takihara orchidometer; 0.52 — coefficient for ellipsoid or prolate spheroid formula; 0.39 — correction coefficient.

$$(8) V=V_{1K}/0.71*0.39$$

where V_{1K} — volume obtained with the aid of Lambert's formula, using external measurement without consideration of the thickness of skin; 0.71 — Lambert's coefficient; 0.39 — correction coefficient.

Statistical analysis of the data was carried out with the aid of the program STATISTICA for Windows v.10. For the assessment of the size of the gonads in

adult males, a time series was constructed. A calculation of mean base and chain-growth rate, as well as a rate of increment, was carried out. The method of enlarging the intervals was utilized (a calculation of mean arithmetic levels of a given period). A calculation of the moving average —mean arithmetic for 3 and 5 years (calculated intervals cross each other), we carried out time series smoothing by 3 and 5 point averages, also we cross-checked the dynamic rows for the presence of any trends with the aid of linear and power functions.

Results

We identified 126 studies following the search carried out, which were published between 1902 and 2018. Further analysis of the publications led to a selection of 33, in which the information contained therein satisfied our set criteria for selection (Table 1). The period of these selected articles ranged from 1902 to 2016. The total number of men involved in the selected studies, based on the method of determination of testicular size, we got the following distribution: 8 (24.24%) — assessment was on autopsy specimens by means of weighing or displacement of water, 4 (12.12%) — determination of linear dimensions, also of cadaveric material, 6 (18.18%) — the use of external linear measurements in living subjects, 7 (21.21%) — determination by means of Prader (6) or Takihara (1) orchidometer and 8(24.24%) — by use of ultrasonography (Figure3).

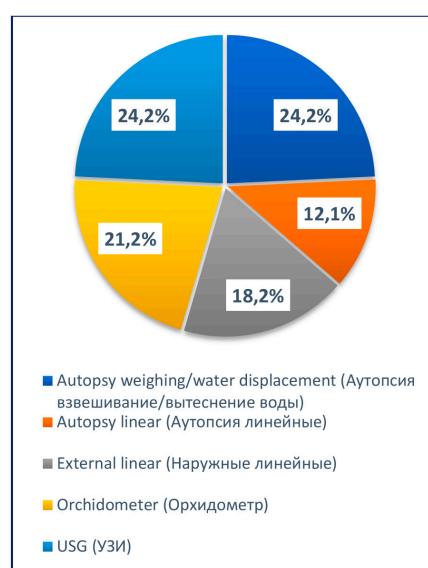


Figure 3. Distribution of studies based on the method of measurement

Рисунок 3. Распределение работ по методам измерения

Table 1. Investigations of the gonadas size in adult males**Таблица 1. Исследования размера наружных половых желез у взрослых мужчин**

Author Автор	Year Год	Country of investigation Страна про- ведеия ис- следования	Number of objects (n) Количество объектов (n)	Age (years) Возраст (лет)	Method of measurement Метод измерения	Dimension Размер	Mean calculated volume (cm ³) Усреднённый вычислённый объём (cm ³)
1	2	3	4	5	6	7	8
Spangaro ^a	1902	Germany Германия	10	19–45	Linear Autopsy Линейные Аутопсия	45x30x23,5 mm (мм)	V=a*b*c*0,71= 22,53
Shultz ^a	1913	Germany Германия	No data Нет данных	≥18	Linear Autopsy Линейные Аутопсия	42,5x27,5x21 mm (мм)	V=a*b*c*0,71=17,43
Mita ^a	1914	Germany Германия	No data Нет данных	≥18	Linear Autopsy Линейные Аутопсия	38x24x23 mm (мм)	V=a*b*c*0,71=14,89
Romeis ^a	1926	Germany Германия	No data Нет данных	≥18	Weighing Autopsy Взвешивание Аутопсия	19,6 g (г)	V=m/1,038=18,88
Roessle and Roulet ^a	1932	Germany Германия	>500	21–60	Weighing Autopsy Взвешивание Аутопсия	17,75 g (г)	V=m/1,038=17,1
Peter et al. ^{a,e}	1938	Germany Германия	No data Нет данных	19–45	Weighing Autopsy Взвешивание Аутопсия	18 g (г)	V=m/1,038=17,34
Schonfeld and Beebe [31]	1942	USA США	125	18–25	Orchidometer “Prader” Орхидометр “Prader”	16,27 ml (мл)	V=V Pr*0,816=13,28
Olesen ^{c,d}	1948	Denmark Дания	140	≥18	Weighing Autopsy Взвешивание Аутопсия	21 g (г)	V=m/1,038=20,23
Hansen ^b	1949	Denmark Дания	33	≥18	Linear. Ellipsoid formula (minus skin) Линейные Формула Эллипсоида (минус кожа)	11,75 cm ³ (cm ³)	V=V ₁ /0,52*0,71=16,04
Lambert [32]	1951	Sweden Швеция	54	42	Linear. Lambert’s formula (minus skin) Линейные Формула Lambert (минус кожа)	20,8 cm ³ (cm ³)	V=20,8
Hansen and Torben [33]	1952	Denmark Дания	844	≥20	Linear. Lambert’s formula (minus skin) Линейные Формула Lambert (минус кожа)	17,35 cm ³ (cm ³)	V= 17,35

1	2	3	4	5	6	7	8
Chang et al. [34]	1960	China Китай	83	20–59	Water displacement. Autopsy <i>Вытеснение воды</i> <i>Аутопсия</i> Linear. Lambert's formula. <i>Линейные</i> <i>Формула Lambert</i>	10,06 ml (мл)	V=10,06
Rundle and Sylvester [35]	1962	UK Великобритания	No data Нет данных	18–30	31 cm ³ (cm ³)	V=V ₁ /0,71*0,39=17,03	
Farkas [36]	1971	Czechoslovakia Чехословакия	176	18–20	Length (длина) – 46,27 mm (мм) Width (ширина) – 27,72 mm (мм)	V=a*b ² *0,39=13,87	
Zachman et al. ^e	1974	Switzerland Швейцария	No data Нет данных	18–19	Orchidometer Prader <i>Орхидометр</i> <i>Prader</i> Weighing Autopsy <i>Взвешивание</i> <i>Аутопсия</i>	18,6 ml (мл)	V=V Pr*0,816=15,18
Johnson et al. [37]	1984	USA США	89	21–50	Orchidometer Prader <i>Орхидометр</i> <i>Prader</i>	18,05 g (г)	V=m/1,038=17,39
Wang et al. [38]	1985	China Китай	1239	19–53	Water displacement. Autopsy <i>Вытеснение воды</i> <i>Аутопсия</i>	17 ml (мл)	V=V Pr*0,816=13,87
Handelsman and Staraj [39]	1985	Australia Австралия	495	18–60	Autopsy <i>Вытеснение воды</i> <i>Аутопсия</i>	18,33 ml (мл)	V=18,33
Ajmani et al. [40]	1985	Nigeria Нигерия	269	18–23	Length (длина) – 46,53 mm (мм) Width (ширина) – 31,72 mm (мм)	V=a*b ² *0,39=18,26	
Centola et al. [41]	1987	USA США	83	35,7	Orchidometer Takihara <i>Орхидометр</i> <i>Takihara</i>	24,8 ml (мл)	V=V Th/0,52*0,39=18,6
Giwercman et al. [42]	1991	Denmark Дания	399	18–50	Weighing Autopsy <i>Взвешивание</i> <i>Аутопсия</i>	19,3 g (г)	V=m/1,038=18,59
Jit and Sanjeev [43]	1991	India Индия	302	18–60	Linear Autopsy <i>Линейные</i> <i>Аутопсия</i>	36,62x25,41x23,77 mm (мм)	V=a*b*c*0,71=15,7
Lenz et al. [44]	1993	Denmark Дания	422	18–59	US-ellipsoid formula УЗ-формула эллипсоида	14,1 cm ³ (cm ³)	V=V ₁ /0,52*0,71=19,25
Spyropoulos et al. [45]	2002	Greece Греция	52	19–38	US-ellipsoid formula УЗ-формула эллипсоида	16,9 cm ³ (cm ³)	V=V ₁ /0,52*0,71=23,08
Tomova et al. [46]	2010	Bulgaria Болгария	620	18–19	Orchidometer Prader <i>Орхидометр</i> <i>Prader</i>	15,58 ml (мл)	V=V Pr*0,816=12,71
Bahk et al. [25]	2010	S.Korea Ю.Корея	1319	19–27	US-Lambert's formula УЗ-формула Lambert	18,2 cm ³ (cm ³)	V=18,25

1	2	3	4	5	6	7	8
Aslan et al. [47]	2011	Turkey Турция	1132	19–30	Orchidometer Prader <i>Орхидометр Прадер</i>	22 ml (мл)	V=V Pr*0,816=17,95
Pilatz et al. [48]	2013	Germany Германия	207	18–60	US-Lambert's formula УЗ-формула <i>Lambert</i>	18,54 cm ³ (cm ³)	V=18,54
Foresta et al. [49]	2013	Italy Италия	776	18–19	US-ellipsoid formula УЗ-формула <i>эллипсоида</i>	14,9 cm ³ (cm ³)	V=V ₁ /0,52*0,71=20,34
Condorelli et al. [50]	2013	Italy Италия	78	23–45	US-ellipsoid formula УЗ-формула <i>эллипсоида</i>	15,2 cm ³ (cm ³)	V=V ₁ /0,52*0,71=20,75
Shalaby et al. [51]	2015	Egypt Египет	2000	21–40	Orchidometer Prader <i>Орхидометр Прадер</i>	21,1 ml (мл)	V=V Pr*0,816=17,22
Hart et al. [21]	2015	Australia Австралия	403	19–22	US-ellipsoid formula УЗ-формула <i>эллипсоида</i>	15,2 cm ³ (cm ³)	V=V ₁ /0,52*0,71=20,75
Tikhonov [52]	2016	Russia Россия	82	18–40	US-prolate spher- oid formula УЗ-формула <i>вытянутого сфера</i>	15,4 cm ³ (cm ³)	V=V ₁ /0,52*0,71=21,03

Comment: a from Lambert, 1951; b from Hansen, 1952; c from Short, 1984; d from Giwercman, 1991; e from Jit, 1991

Примечания: а из Lambert, 1951; б из Hansen, 1952; в из Short, 1984; д из Giwercman, 1991; е из Jit, 1991

According to the results of the calculations with the aid of the standardizing formulae, we found the calculated mean volume of each study (Figure 4). After statistical analysis of the data, the weighted arithmetic mean value was 17.43 ± 5.64 ; 95% CI (17.32, 17.54). The coefficient of variation obtained was 32.34%, and this confirms the uniformity of the sizes within the period under investigation. Therefore, based on the data obtained, there were

no statistically significant tendencies observed in the change of volume of testes for the last century.

Discussion

Testicular volume in adults is mainly determined by the pool of differentiating germ cells as well as Sertoli cells. Many studies have established a direct quantitative relationship between the above-mentioned components of the testes and the

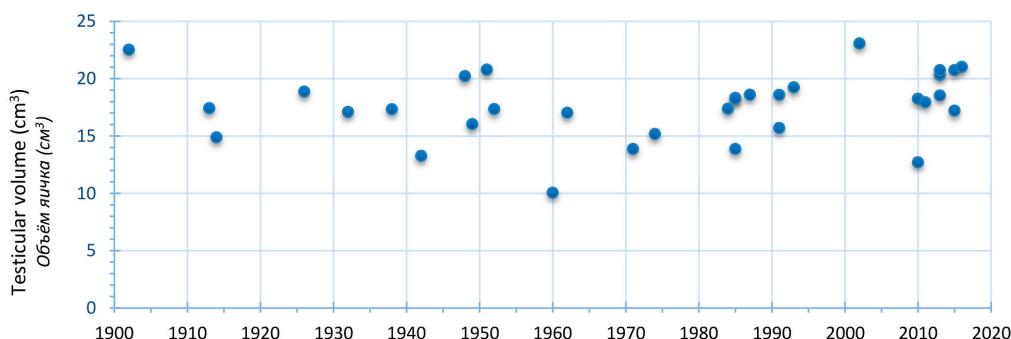


Figure 4. Homogenized results of investigations of the volume of the testes over time in years
Рисунок 4. Гомогенизированные результаты исследований объема яичка по годам

outcome of germ cells. Considering the tendency worldwide of a reduction in the concentration of spermatozoa, it would have been logical to expect a similar tendency of reduction in testicular volume. As far as we know, such findings at present are absent.

Giwercman et al. (1991) made such an assumption. However, when they compared results from cadaveric studies from Olesen (1948), which were done at the same facility 40 years earlier, there was no statistically significant reduction in testicular size [42].

Carrying out of retrospective analysis is problematic for a couple of reasons. The main problem lies in the fact that there is no standardization of the methods employed in measuring testicular dimensions. Earlier studies were based often on the assessment of cadaveric material. The authors seldom commented on the extent of dissection of the testes, often weighed the specimens with the epididymis (Spangaro, 1902; Stieve, 1930 from Lambert, 1951 [32]). Part of dimensional studies were carried out after fixation of the specimens [53].

As recently as the 1970s, in clinical practice, the testicular size was compared to different objects of similar shape (peas, beans, grapes, hazelnuts), or subjectively characterized by authors as "small-normal" [29].

In 1942 Schonfeld and Beebe were the first to invent an orchidometer, which consisted of 23 ellipsoid models of known volume. Comparison of the testis during palpation with the model of similar size allowed for estimation of testicular volume [31]. The Prader orchidometer, which was proposed in 1966 and became popular, remaining widely in use up to date, was based on the same principle [54]. Its simplicity and low cost popularized the method among researchers and clinicians alike. A series of comparative volumetric studies indicated that a high correlation of volume between the estimated and actual. This notwithstanding, the estimated volumes were found eventually to be higher, besides, there were high reproducibility errors inherent in the process of measurement [55–62].

External measurements with the aid of a ruler or callipers were also actively employed for the evaluation of testicular size [32, 33, 35, 40, 63–70]. In the event of direct measurement of testicular size with the aid of rulers, an unavoidable error arises as a result of the inclusion of the skin and testicular tunics. Therefore, some authors suggested the subtraction of the duplication of the scrotal skin from the results of such measurements [32, 33].

The Hynie orchidometer [30] was quite popular and widely used among clinicians. The basis for

calculation for this device lies in the measurement of the length of the testis (it's longest dimension-d) and applying this in the formula $V=d^3/4$ to determine the volume of the testis [29]. It was quite predictable that comparative volumetric investigations will reveal wide margins of error using this device [55]. Another type of orchidometer was introduced by Takihara in 1983. This device consists of stencil ellipsoid rings of different sizes. The corresponding size to the testis was slipped over the gonad with the scrotal skin stretched. The calculation of the volume using this device is based on the formula of a prolate spheroid: $V=0.52*a*b^2$ [71].

In contemporary research as well as in current clinical practise, we often employ ultrasonography for the assessment of testicular volume. This method allows us to determine more accurate dimensions due to clear visualization. However, just as with the external linear measurements, there was no consensus on the most appropriate formula for calculating the volume. Most often we employ already installed formulae on the ultrasound machines for calculating the volume of an ellipsoid: ($V=0.52*a*b*c$) or that of a prolate spheroid: ($V=0.52*a*b^2$) [48]. In recently published recommendations, the working group of the European Society of Urogenital Radiology agreed to use Lambert's formula ($V=0.71*a*b*c$), in computing the volume of the testis during ultrasound investigations, as the closest in correlation to the actual testicular volume [72].

Another important factor that makes retrospective analysis difficult to carry out is the fact that testicular size varies greatly among different age groups. Most contemporary studies focus on the measurement of testicular volume in children and adolescents as a factor of sexual development [46, 61, 62, 66, 67, 69, 73–91]. The size of gonads after puberty alters only insignificantly. Testicular volume will tend to reduce only after 60 years of age [48, 53, 92–95].

Most often researches focus their investigations on certain disease states of the male reproductive system which have the potential to affect the size of the gonads. This may be a selection based on fertility [28, 96, –100], the presence or absence of a varicocele [41, 81, 99, 101, 102], cryptorchidism in the past medical history [68, 103] or indeed from andrological patients [26, 60].

Finally, some researches point to the fact that there are racial and ethnic differences in the size of gonads in adult males [71, 79, 104].

In the current study, we analyzed the volume of the testes in healthy men aged 18–60 years

using available publications in the literature. After the selection of data that satisfied the required criteria, we homogenized the given volumes. The measurement of testicular volume based on the Archimedes principle of displacement of water was considered the most accurate. The density of the testis without the epididymis is 1.038 g/cm³ [94]. This parameter was used to calculate the volume in the studies that were carried out through a measurement of the mass of the testis (Formula 1).

Even though the shape of the testis is like a prolate spheroid, many studies indicate that more accurate results can be obtained using Lambert's formula with a coefficient of 0.71[32, 55, 59, 105, 106]. For this reason, we used Lambert's formula for calculation of testicular volume, whose linear dimensions are known (Formula 2 and 3).

In his original article, Lambert pointed out the importance of subtracting the skin thickness when calculating testicular volume with the aid of external linear measurements [32]. In studies where the authors subtracted the skin thickness but then calculated the testicular volume using the formula of an ellipsoid, we recalculated by employing Lambert's coefficient (Formula 4).

V. Dornberger and G. Dornberger [55] in their studies based on comparative volumetric investigations suggested a correction coefficient of 0.39 in the ellipsoid formula during external measurements which were carried out without taking into account the thickness of the skin. We utilized this in formula 5. In the case where the authors calculated the volume of the testis using Lambert's formula without subtracting the skin thickness, we employed formula 8. The principle

behind the Takihara orchidometer is based on the ellipsoid formula. The idea behind this method is similar to that of external linear measurements without correction for skin thickness. For the determination of testicular volume in such cases we employed formula 7.

The margin of error with the use of the Prader orchidometer varies widely depending on the age and volume of the testis [61, 85]. For volume calculation, we used the adjusted coefficient of 0.816 which was suggested by Sakamoto [59] (formula 6).

Ultrasound results were recalculated using Lambert's formula.

Analysis of the data we obtained confirms the absence of any kind of significant global secular trends in the testicular size of adult males. This does not correlate with the concept of a global tendency towards a reduction of sperm concentration in the ejaculate.

There is a possibility that the factors which have an inhibitory action on spermatogenesis, do not necessarily lead to a reduction in the number of Sertoli and germ cells, i.e. the weight and volume of the testis, but influences the differentiation of the latter.

Conclusion

In the light of global trends towards reduction infertility, it is necessary to carry out further wide-ranging investigations in order to elucidate the nature of the process. Standardization of methods of assessment of the results will aid in reducing the margins of error and this will assist in the analysis of the existing tendencies.

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