

Is Decreasing Sperm Concentrations a Sign of a General Decay in Fertility Potential?



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Annoying Facts

Reports on imminent or ongoing catastrophes tend to rapidly attain general attention. Without diminishing the gravity of signs of severe changes in the global male reproductive potential, it is essential that the scientific community continuously consider and evaluate the underlying evidence and reasonable alternative explanations. It is also essential to keep in mind that statistical methods do not prove the existence of true differences or relations. The statistical tests only estimate the probability that random variability has caused the observed data: if the probability for random distribution of results to cause the found results is less than 5% it is usually considered statistically significant. Still, in 5 out of 100 random instances results are outside the “reference range.” Furthermore, a reference limit based only on the distribution of results from healthy volunteers (or men with proven fertility) does not represent a limit between normal fertility and subfertility. The distribution of results from fertile men does not disclose anything about the distribution of results from subfertile men.

This chapter is dedicated to elucidating both factors that could constitute alternative explanations to a real decline in human sperm production and factors that could be possible contributors to a true general decline in human sperm production.

Among factors and facts to be considered when evaluating a possible decline in sperm counts is also the meaning of “semen quality,” sperm production, sperm transport, ejaculation, and laboratory techniques. Without taking sufficient attention to such aspects, the risk for mistaken conclusions increases—both for false premonitions and false dismissals of true threats to male reproductive potential.

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What Is Semen Quality?

A very common simplification used in publications investigating male factors and semen analysis results in relation to fertility is the ambiguous term “semen quality.” The meaning of “quality” is a distinguishing characteristic. However, sperm concentration or total sperm count cannot be said to be a distinguishing factor for a man’s fertility potential in the entire range of results. It is true that men with few spermatozoa are less probable to contribute to a “spontaneous” pregnancy (Björndahl 2011), but no exact limit exists. For sperm numbers above, for example, 40 million, there is no direct relation between fertility and sperm number. For instance, 150 million sperm in the ejaculate does not mean a doubled fertility capacity compared to an ejaculate containing 75 million spermatozoa. The WHO semen manual (Cooper et al. 2010) is often misunderstood concerning the distributions of results and assumed reference limits: the distributions of results from fertile volunteers (in male contraceptive studies) only show those distributions, not limits that distinguish between subfertile men from fertile men.

Another misconception is the overuse of sperm concentration as a measure of quality, ignoring that this measure depends on two mainly independent functions: on one hand the production and transport of spermatozoa to the urethra and on the other the secretory function of primarily the seminal vesicles and the prostate. Variation in these functions can be considerable and if sperm production is the primary interest, the total number of spermatozoa is a better measure than the concentration.

Sperm Production

The starting point of spermatogenesis is related to the onset of puberty leading to gonadotrophins release from the pituitary causing high intratesticular androgen levels and the development of immature testicular “strings” into testicular tubuli seminiferi containing germ cells in different stages of development and “nursing” Sertoli cells. Once started, the process with high mitotic activity of spermatogonia and subsequent sperm production appears to continue without major changes even into high age provided the intratesticular androgen levels remain high. After several generations of mitotic divisions, some spermatogonia enter spermatogenesis by entering the meiotic division, where finally four gametes are formed from each immature germ cell. The quantity of sperm production is largely dependent on the number of stem cells and the number of generations of mitotic divisions—two factors that can be assumed to be genetically controlled. Based on the estimation of a magnitude of 50–100 million spermatozoa formed each 24 h, several hundreds of germ cell mitoses would occur every second. This would explain the wide range of sperm numbers that is considered as a sign of normal fertility potential.

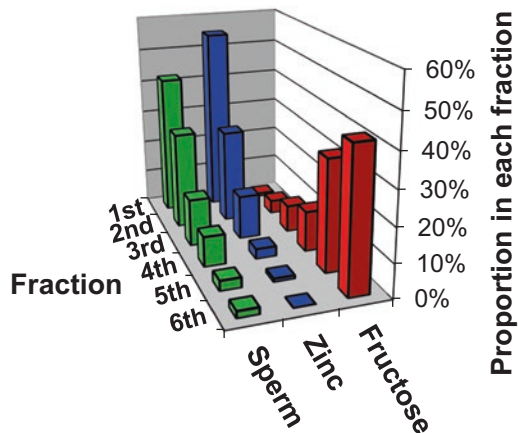
From this point of view, possible factors threatening male reproductive potential would be interaction with the genetic control of spermatogenesis as well as normal pituitary and testicular endocrine functions (including use of anabolic steroids or dietary supplements with similar additions as well as hormone receptor mutations).

Sperm production being continuous requires a functional storage function which is believed to be one main function of the epididymides. The reservoir capacity is however, compared to other animals, limited. A maximum of 2 days of testicular sperm production is estimated to be stored in the cauda epididymis (Bedford 1994). Studies aiming at establishing baseline sperm production indicate that a maximum abstinence time ideally should be 42–54 h (at a maximum up to 60 h), corresponding to 1.75–2.25 days (or a maximum of 2.5 days), if the man has ejaculated every 42–60 h the week preceding ejaculate collection (Amann and Chapman 2009). Ignoring this could lead to difficulties establishing both the true baseline for sperm production and therefore create difficulties determining the effects of interventions like hormonal contraception (Behre et al. 2016).

Ejaculation

The process of sending spermatozoa to the gametes of another individual (i.e., oocytes) is a quite intricate and complicated function. Compared to the situation in water-living animals, mammals like humans have adapted to internal fertilization and fetal development. The process of ejaculations is effectuated by autonomous nerve signals stimulating secretomotor activity in accessory sex glands and contractions of smooth muscle cells in caudal epididymides, vasa deferentia, prostatic land acini, and seminal vesicles. Due to differences in the relation between lumen diameter, the thickness of smooth muscle tissue (wall thickness), and viscosity of fluids, the normal sequence of ejaculation is that spermatozoa are mixed with prostatic fluid and expelled before the emptying of the seminal vesicles (Fig. 1) (Björndahl

Fig. 1 Schematic representation of the relative contribution of spermatozoa (green), prostatic fluid (zinc, blue), and seminal vesicular fluid (fructose; red) in an ejaculate collected with the six ejaculate fractions separate (split-ejaculate technique) (Björndahl and Kvist 2003)



and Kvist 2003). In the natural situation, this is to the advantage of the spermatozoa, since the seminal vesicular fluid, in general, has a mainly negative impact on sperm function (Lindholmer 1973) and sperm DNA protection by chromatin stability (Björndahl and Kvist 1990). The quality of the ejaculation is apparently dependent on the duration and quality of sexual arousal (Pound et al. 2002).

The expulsion of the ejaculate is largely dependent on contractions of the striated muscle tissue surrounding the corpora cavernosa and thereby increasing the pressure in the urethra. The rhythmical contractions of the striated muscle tissue are also dependent on a proper erectile function to increase the urethra pressure and thereby execute an efficient ejaculation.

Any pharmaceutical treatment able to interact with autonomous nerve activity, smooth muscle, or striated muscle contraction is therefore likely to interfere with normal ejaculation. Psychoactive drugs like serotonin uptake blockers are suspected to be able to interact with normal ejaculation, as is antihypertensive drugs like α_1 -adrenoreceptor blockers (Doxazosine) that cannot only increase the risk for retrograde ejaculation but also interfere with sperm transport and emptying of accessory sex glands leading to azoospermic ejaculation or even “dry ejaculation” (orgasm without antegrade ejaculation, often mistaken for retrograde ejaculation if the presence of sperm in postorgasmic urine has not been investigated). Peripheral nerve damage, not uncommon in poorly controlled diabetes mellitus, is also a possible cause for interference with normal ejaculation.

Laboratory Techniques

It is a strength of the recent study indicating a temporal decline in sperm numbers that attempts have been done to eliminate publications based on substandard laboratory techniques by only including studies based on haemocytometer measurements of sperm numbers (Levine et al. 2017). By doing this, a number of common sources of errors are minimized. Studies using low volume chambers have a higher risk for using subsampling with aliquots with poor representativity of the entire ejaculate. Furthermore, counting still motile sperm in undiluted ejaculates also increases the risk for technical errors in assessing the sperm number, and counting less than 400 spermatozoa increases the influence of random errors to result in errors in the results (Fig. 2). To reduce the influence of random errors it is essential to compare replicate counting of at least 200 spermatozoa (Björndahl et al. 2016).

With regards to the assessment of sperm motility, the assessment of progressive motility, a controlled and constant temperature is important. Room temperature is not a defined temperature and within the usual range of temperatures expected to be that temperature, the velocity of motile spermatozoa will vary. The recommendation is therefore to have a controlled temperature close to 37 °C.

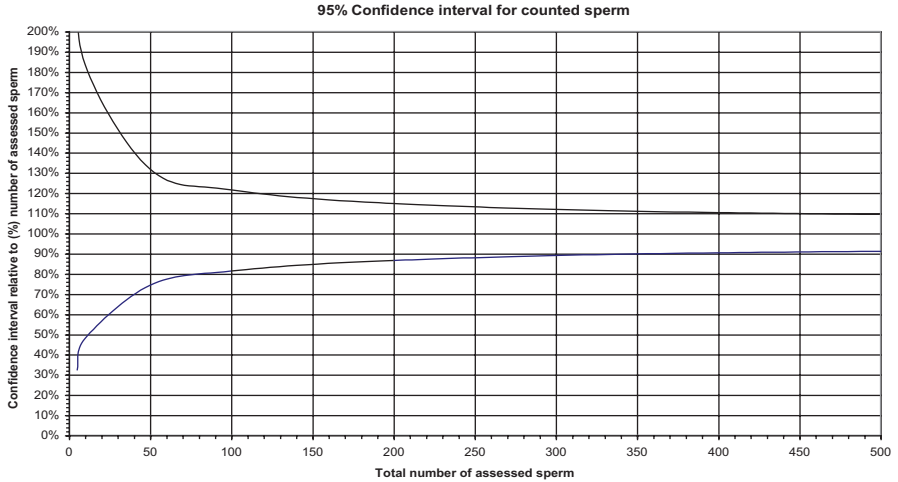


Fig. 2 Graph showing the uncertainty in results (95% Confidence Interval) depending on the total number of observations (spermatozoa counted) to obtain the result

Discussion and Conclusions

The ideal studies for global assessment of a possible decline in sperm numbers would be studies where investigated samples have been collected after 3 days of daily ejaculations to exhaust the epididymal sperm storages. Without doing that the obtained sperm numbers are not directly related to sperm production but a combination of the number or stored spermatozoa and the daily production. The time for sexual abstinence cannot replace systematic exhaustion of epididymal sperm storages, and mathematical adjustment of sperm counts based on sexual abstinence before sample collection cannot do that either. Furthermore, the mathematical adjustment is based on an average with uncertainty, and the adjusted value then is burdened with both the basic uncertainty augmented with the added uncertainty due to the variation in the adjustment.

Furthermore, what does it mean that the average number of sperm has decreased among investigated men? Since all included studies are based on investigations of men recruited under different circumstances from different populations, there is a possibility that variation in recruitment or population may be a contributing factor to the observed differences. There could also be a shift in participants’ frequency of ejaculations before the investigated ejaculate, irrespective of the “days of abstinence” before the collection of the investigated ejaculate.

Few studies have followed the same men. There are indications that men without fertility problems may retain sperm production and functions better than men with fertility problems (Björndahl 2013). Following the same cohort of men could indicate age-related decline while examining birth-cohorts of men would be better to unravel temporal changes based on year of birth.

Although studies going back to early 1990s have indicated a possible ongoing decline in sperm production (Carlsen et al. 1992) contemporaneous studies of population fertility (based on Time-To-Pregnancy) have indicated that at that time a decrease in sperm number had not yet had an impact on the population fertility (Akre et al. 1999; Scheike et al. 2008).

From a global perspective, a decline was apparent in Western countries. In other parts of the world, a similar pattern of decline could not be shown. An important aspect of the latter is, of course, a lack of published investigations over time to the same extent as in Western countries. However, it still raises questions if a decline is mainly a problem in Western countries—or if it is a matter of changes of ethnical/genetical contributions to investigated populations in these countries. There is a general lack of knowledge if there are genetic differences (e.g., testicular size and thereby capacity for spermatogenesis) in different parts of the world, or if other factors like nutrition and exposure to gonadotoxic substances and pharmaceuticals may contribute both to differences and decline.

In conclusion, a general decline has been found in ejaculates examined in Western countries. If this is due to a true decline leading to a decline in fertility potential remains to be proven. To do that, more focused studies are needed, with a design to clearly define recruitment and status of participants, minimize bias by variability in sperm storage, and laboratory techniques.

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