Is vasectomy harmful to health?

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SUMMARY

Since the late 1960s, vasectomy has been a popular and widely used form of contraceptive in Britain for couples who do not want to have any more children. However, throughout the past decade there has been considerable concern about the safety of this procedure. This paper reviews the current opinion on the possible health considerations associated with this operation and shows that the latest news is mostly reassuring.

Introduction

VASECTOMY is a popular contraceptive option for couples who have completed their families. It has been widely used in Britain since the late 1960s. The failure rate is about 0.2 per 100 women years[1] and is mostly caused by spontaneous recanalization.[2,3]

For some years, and particularly throughout the 1990s, considerable concern has been expressed about the safety of the procedure. There have been scares about associations with cardiovascular disease and cancer of the testis and prostate. In addition, the local effects on the reproductive tract are not completely understood and a small percentage of patients develop chronic epididymal pain or discomfort. Low fertility following vasectomy reversal has been a problem that can now often be overcome by in vitro fertilization techniques. This article reviews current opinion on all these health concerns and shows that the latest news is mostly reassuring.

Method

Over the past decade, the author has written a number of papers on the sequelae of vasectomy and, prior to starting work on the present article, was already familiar with much of the literature. For this review, the author's existing reference database was supplemented by references obtained by a Bath Information and Data Services (BIDS) computerized search from 1986 to 1996. All papers showing the word 'vasectomy' in the title, keywords or abstract were considered. For most citations, an abstract was available. When the title or abstract suggested that the paper was relevant to the review, the full paper was obtained from the Glasgow University Library or through the inter-library loans service. For each article, judgements were made about the scientific basis of the conclusions and the usefulness of the findings for the review. Care was taken to ensure that, for controversial topics, both sides of the debate were fairly and adequately represented. Reference lists cited in papers were scrutinized to ensure that all relevant papers were included in the review.

Cardiovascular disease

The evidence that vasectomy may predispose to cardiovascular disease has been reviewed by Campbell.[4] In the 1970s, Clarkson and Alexander claimed that atheromatous plaques in large blood vessels were more severe in vasectomized monkeys than in sham-operated monkeys fed standard or atherogenic diets.[5,6] Repeat experiments,[7,8] in contrast, gave negative findings. Clarkson *et al*[8] attributed the discrepancy to the small numbers of monkeys in their earlier work. Other studies have shown evidence of increased arterial disease in vasectomized monkeys,[9] rabbits,[10] and rats[11] fed an atherogenic diet.

Alexander's group[12] also claimed that the ophthalmic arteries more commonly showed disease in vasectomized patients, but a second investigation again gave negative results.[13] The controversy about an association between vasectomy and atheroma continued through the 1980s, and Campbell *et al*,[14] using Doppler ultrasound techniques, indicated that vasectomized patients may have a higher risk of peripheral artery disease. However, this finding may have arisen from inadequate matching of blood pressure between patients and controls.

In recent years, several long-term studies of vasectomized patients have produced no evidence of increased cardiovascular disease;[15-19] indeed, it may be less common in the vasectomized population.[15, 17, 19] It is difficult to reconcile the results of these studies with the observations of arterial disease in vasectomized animals fed an atherogenic diet. While the news from the human studies is reassuring, continued monitoring is essential, particularly now that the first cohorts of vasectomized patients are reaching retirement. Generally, diabetic patients are at high risk of vascular problems. The effect of vasectomy in this group has not been specifically studied but there are no reports of adverse effects, although a small amount of experimental work has indicated that vasectomy promotes arterial disease in diabetic monkeys.[20, 21]

Testicular cancer

A link between vasectomy and testicular cancer has not been substantiated. Thornhill *et al*[22] and Cale *et al*[23] thought that vasectomy might accelerate the growth of testicular tumours. Thornhill *et al*,[22] in a five-year review of Irish health statistics, found three patients in whom a relatively uncommon variety of testicular cancer had been diagnosed within a few weeks of vasectomy. Cale *et al*,[23] in an industrial area of Scotland, found a cluster of eight men also diagnosed as having testicular cancer shortly after vasectomy, but did not report the histological type. Subsequent large studies by Nienhuis *et al*,[18] Hewitt *et al*,[24] and Moller *et al*,[25] however, have found no evidence that vasectomy predisposes to cancer of the testis. In addition, Moller *et al*[25] found nothing to support the suggestion that vasectomy might accelerate the growth of early testicular cancers.

Prostate cancer

Concern about an association between vasectomy and cancer of the prostate intensified in 1990 with the publication of two case-control studies in the United States (US),[26,27] which supported an earlier report of such a link.[28] Since then, several other American case-control studies[29-32] and prospective and retrospective cohort studies[33,34] have been published. In addition, a letter has been printed summarizing the results of an unpublished case-control study.[35]

The aetiology of prostate cancer remains poorly understood.[36] In developed countries it is the third commonest malignancy in men, after lung and colorectal carcinomas. The increase in the risk of developing prostate cancer after vasectomy, as estimated in each of the above studies, is summarized in Table 1.

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Table 1. The estimated increase in risk of developing prostate cancer after vasectomy in various studies.

Study	Relative risk	Long-term risk
Honda et al [28]	1.4	2.2 after 20–29 years 4.4 after 30 or more years
Rosenberg et al[26]	5.3 (non-cancer controls) 3.5 (cancer controls)	No further increase in risk in long term
Mettlin et al[27]	1.7	2.2 after 13–18 years
Sidney et al[29]	No risk detected	No risk detected
Spitz et al[35]	1.6	2.2 after 27 years
Hayes et al[30]	None overall under 36 years of age at vasectomy.	In whites: 1.7 after 20 years, 2.2 if In blacks: no risk detected
Giovannucci et al[33]	1.56	1.85 after 22 years
Giovannucci et al[34]	1.56	1.89-2.06 after 20 years
Rosenberg et al[31]	No risk detected	No risk detected
John et al[32]	No risk detected	No risk detected

Several studies[27,28,30,33-35] have indicated that the risk of developing prostate cancer after vasectomy may be doubled in the long term. Guess[37] has reviewed possible biases in these studies. In contrast, the work of Sidney *et al*,[29] and the most recent studies by Rosenberg *et al*[31] and John *et al*,[32] have indicated no association of prostate cancer with vasectomy.

All the above studies were conducted in the US, where prostate cancer is common. There is little information about a link between vasectomy and prostate cancer from other parts of the world. Hsing *et al*[38] reported an increased risk of 2.0–6.7 times in a case-control study of vasectomized men in China, where prostate cancer is infrequent. However, the authors were concerned about detection bias in their study. It is reassuring to note that the only studies from Europe, retrospective cohort studies using record linkage in Britain and Denmark, have not detected any association between vasectomy and prostate cancer.[18, 25]

The debate is unresolved. The fact that an association between vasectomy and prostate cancer is not proven has been endorsed by a World Health Organization working party.[39] Even if a relationship between vasectomy and prostate cancer is proven, further investigation would be required to determine if vasectomy causes prostate cancer or whether vasectomized men are more exposed to the real causal agent.[36] Possible mechanisms by which vasectomy might cause prostate cancer are speculative, but might involve hormonal changes, immunological responses or failure of growth inhibitors to reach the prostate owing to obstruction of the reproductive tract.[40]

Since 1990, several studies have suggested that prostate cancer might be up to twice as common in vasectomized men.[27,28,30,33-35] When advising patients considering vasectomy, it might be useful to give perspective to the possible risk. Prostate cancer remains a disease of elderly men; in the 65–74 age group, about 3 men per 1000 in Britain develop prostate cancer in a year. The mortality rate from prostate cancer in this age group is about 1 per 1000. If the risk were doubled for vasectomized men in the United Kingdom, this would mean that 6 vasectomized men per 1000, aged 65–74, would be expected to develop prostate cancer per year. The chances of dying from another cause during the course of a year at this age are five times greater.[41]

Local effects on the reproductive tract

The effects of vasectomy on the reproductive tract itself are not fully determined. They are difficult to study in man, and animal models have been invaluable in deepening the understanding of possible local sequelae. The local effects of vasectomy show marked variations between species.

Pressure in the reproductive tract

Following vasectomy, the testis continues to produce spermatozoa and fluid which pass into the obstructed epididymis and ductus deferens and cause a rise in intraluminal pressure. Evidence from studies using hamsters indicates that the rise in intraluminal pressure occurs in the tail of the epididymis and the obstructed ductus deferens;[42] the peristaltic activity of myoid cells around the epididymal duct is probably responsible for preventing a pressure rise in the duct closer to the testis. The result of this rise in pressure depends on the species. In rabbits and guinea pigs, the lower epididymis may become grossly distended.[43,44] In contrast, rats and hamsters show little distension but exhibit early rupture at the epididymal tail or vasectomy site, with a leakage of spermatozoa into the surrounding tissues.[42,45,46] The extravasated spermatozoa form a chronic inflammatory mass: a sperm granuloma. Howards and Johnson[42] have shown that, in hamsters, granuloma formation returns the intraluminal pressure to prevasectomy values. In vasectomized men, distension of the epididymal duct occurs in most patients,[47-49] and granuloma formation is common.[47,50]

Sperm granuloma

Sperm granulomas are cream-coloured ovoid or irregularly-shaped masses which, on histology, resemble the granulomas of tuberculosis.[51] The chronic inflammatory response is probably stimulated by fatty acids, released from degenerating spermatozoa, which are similar to the mycolic acid of tubercle bacilli.[52] The lesions consist of a mass of degenerating spermatozoa surrounded by a layer of macrophages, surrounded in turn by a layer of vascular connective tissue rich in lymphocytes and plasma cells.[53] They are important sites of sperm phagocytosis[53] and of presentation of spermatozoal autoantigens to the immune system.[54] They are likely to be responsible, at least in part, for the stimulation of the antisperm antibody production seen in about 60 per cent of patients following vasectomy.[55,56]

Immune response to spermatozoa

Spermatozoa are autoantigenic because they first form at puberty, long after immunological tolerance to other body components

has formed. Normally, spermatozoal antigens are isolated from the immune system by epithelial barriers along the reproductive tract, but these may be damaged following vasectomy.[57] Serum antisperm antibodies are well-documented in vasectomized men.[55,56] Evidence from the rat suggests that the immune response is mediated via the regional lymphatics and lymph nodes rather than via the blood vessels and spleen.[46,58] Information on cell-mediated immunity to spermatozoal autoantigens is scant but, in vasectomized rats and sheep, helper T-lymphocytes are found in the granuloma wall.[53,59] In vasectomized rats, the regional testicular lymph nodes show a little enlargement of the thymus-dependent cortex[58] and there are changes in the distributions of helper and cytotoxic T-lymphocytes in the epididymal epithelium and interstitium.[60]

Adverse effects of antisperm antibodies

Antisperm antibodies are implicated in the low success of vasectomy reversal.[61,62] Even in the best units, the results of microsurgical vasovasostomy can be disappointing. Patency and pregnancy rates decrease with time after vasectomy. With a reversal up to three years after vasectomy, about 97% of patients regain spermatozoa in the ejaculate and about 76% are fertile. With a reversal 15 or more years after vasectomy, only about 71% of patients show spermatozoa in the ejaculate and only about 30% are fertile.[63] Spermatozoa can be agglutinated or immobilized by antisperm antibodies gaining access to the reproductive tract. Attempts were made to improve fertility in these patients by treatment with anti-inflammatory drugs,[62] but recently the technology has become available to overcome the problem by in vitro fertilization.[64-66]

As well as impairing spermatozoal function, there is unproven speculation that antisperm antibodies could lead to systemic disease. Those concerned about increased cardiovascular disease following vasectomy believed that atheroma could be caused by circulating immune complexes of spermatozoal antigens and antisperm antibodies damaging blood vessel walls.[5] There was also worry that such immune complexes could deposit in kidney glomeruli and cause renal damage. Despite some evidence of immune complex deposition in renal glomeruli of vasectomized rabbits and monkeys,[67,68] no increased incidence of kidney or other auto-immune disease has been found in man.[19]

Allergic reactions to protamine are a possible risk of antisperm antibody formation following vasectomy. Many antisperm antibodies are raised against protamines, a group of proteins found in spermatozoal nuclei.[69] Salmon protamine is administered to reverse the anticoagulant effect of heparin in patients undergoing cardiac catheterization and cardiothoracic or vascular surgery. There is a potential risk that the protamine might interact with the antibodies and produce an adverse reaction. A case of anaphylaxis has recently been reported in a vasectomized patient having cardiothoracic surgery,[70] but it is unclear whether the vasectomy was responsible.[71]

Effect of vasectomy on the testis

The effect of vasectomy on the testis in man and animals is controversial. Many researchers and clinicians have believed that vasectomy has no effect on the testis. This is not so. Several groups have reported histological changes in testicular biopsies from vasectomized men.[72-79] Despite the abnormalities, some of these men have been fertile after vasectomy reversal.[75,77,78] The presence of interstitial fibrosis in biopsy specimens collected at vasovasostomy may indicate a poor prognosis for subsequent fertility.[77] Jarow *et al*[79] were unable to show any correlation between the presence of serum antisperm antibodies and testicular damage. The mechanism by which testicular changes occur after human vasectomy is unknown. Animal models have been particularly useful in illustrating possible ways in which the testis might be affected.

Temporary depression of spermatogenesis. Temporary depression of spermatogenesis following vasectomy is reported in dogs, and is perhaps the result of raised intraluminal pressure.[80-83] Normal function seems to return after a few weeks.[80,82 83]

Obstruction of head of epididymis. Following vasectomy, an association between degeneration of seminiferous tubules and sperm granuloma formation in the epididymal head has been reported in the vasectomized rabbit, hamster,[43] and rat.[84] It seems that granulomas in the epididymal head are unable to accommodate the spermatozoa and fluid produced by the testis. The consequent rise in intraluminal pressure damages the seminiferous epithelium and leads to tubular degeneration and collapse. In the rat[84] there was good evidence that the atrophy was the result of elevated pressure, as some testes were tense, blanched, and swollen to about twice their normal size. Clearly, human testes, having a much tougher tunica albuginea, do not show such marked swelling after vasectomy, but the possibility that they show pressure-mediated damage has not been excluded.

Autoimmune orchitis. In addition to mechanical damage, vasectomy may induce autoimmune orchitis. In this condition, a cell-mediated immune response to spermatozoal antigens generates T-lymphocytes which invade and destroy the seminiferous epithelium. Tung[85] reported autoimmune orchitis in vasectomized guinea pigs. In contrast, Muir *et al*[86] considered that the tubular damage in their material probably had a mechanical aetiology. Recent work[87-89] on guinea pigs three years after unilateral vasectomy has shown that testicular damage was confined to the vasectomized side, and that only some of the atrophic testes showed lymphocyte infiltration. These findings suggest that the damage was primarily mechanical but that it stimulated a subsequent immune response.

Immune complex deposition. Bigazzi *et al*[90] have detected immune complexes containing antisperm antibodies in the basement membrane of the seminiferous epithelium of vasectomized rabbits. The significance of this finding for the health of the testis has not been determined.

Testosterone production. The effect of vasectomy on interstitial cell function is poorly documented and has received little attention in recent years. Evidence on hormone levels has been conflicting but there is a general consensus that they are within the normal range following vasectomy.[91] Wild claims have been made that vasectomy lowers testosterone production and leads to premature ageing[92] or erectile dysfunction;[93] these claims are without sound scientific foundation. Psychological problems following vasectomy may, however, lead to erectile dysfunction[94].

Effect of vasectomy on the epididymis and obstructed ductus deferens

The effect of vasectomy on the human epididymis and ductus deferens has recently been reviewed in detail.[95] Surgeons report that dilatation of the epididymal duct after vasectomy is common.[47-49] Granulomas at the vasectomy site are occasionally troublesome but often relieve intraluminal pressure and, by reducing epididymal disruption, improve the success of vasectomy reversal.[96] Ultrasound scans of the scrotum have shown that epididymal enlargement and cyst formation frequently follows vasectomy;[97,98] the cysts were likely to have been sperm granulomas.

Sperm granuloma formation in the epididymis can disrupt the continuity of the epididymal duct and impair the chances of successful vasectomy reversal.[99] Work in rats has indicated that sperm granulomas increase in number with time after vasectomy, and form progressively closer to the testis.[100]

Animal models, particularly in rats, rabbits, and guinea pigs, have also been useful in suggesting why some men show more epididymal distension and granuloma formation than others. In the vasectomized rat, distension of the reproductive tract is minimal and the sperm escape into a large granuloma at the vasectomy site or lower epididymis.[46] In contrast, rabbits[43] and guinea pigs[44] may show gross distension of the epididymal duct and minimal granuloma formation. Certain guinea pigs, however, show neither gross distension nor granuloma formation, but do show many intraluminal macrophages.[44] These macrophages probably degrade the spermatozoa to soluble products which are absorbed by the epididymal lining, thus preventing distension and granuloma formation. Intraluminal macrophages are also seen in other species including man.[101,102] It is likely, but still not proven, that those patients with little epididymal distension or granuloma formation show intraluminal phagocytosis of spermatozoa by macrophages.

Chronic intrascrotal pain and discomfort

Epididymitis has been reported in up to 6% of vasectomized patients.[2,103-108] This is not usually caused by infection and is often called 'congestive epididymitis'. The subject has recently been reviewed by McDonald.[95] The pain is usually a dull ache in the scrotum, which may be exacerbated by sexual excitement and ejaculation. The symptoms usually occur in the first few months after vasectomy and are associated with distension and granuloma formation in the epididymis and ductus deferens. There is no report of the testis itself being painful after vasectomy.

While many patients develop structural changes in the reproductive tract after vasectomy, only a minority experience discomfort. The pain may result from scar tissue forming around small nerves.[109,110] The condition usually settles with conservative management; anti-inflammatory drugs such as ibuprofen and indomethacin may be useful,[105,108,110-112] as may a scrotal support.[108,112] Occasionally the symptoms fail to settle and there is progressive induration, tubular distension, and granuloma formation in the epididymis. This chronic condition is often called 'post-vasectomy syndrome' and may require excision of the epididymis and obstructed ductus deferens.[110,113]

Conclusion

When counselling patients considering vasectomy, it remains paramount that they are advised that it is frequently not possible to reverse a vasectomy, and that attempts to do so may require techniques that cannot be funded by the National Health Service. Patients should be warned that a small number of people experience scrotal discomfort in the longer term following vasectomy, but that this usually soon settles. They should be told that, while some studies have suggested a small increased risk of prostate cancer after vasectomy, it is not proven, and that several surveys, including two of the most recent, have detected no increase in risk. They can be reassured that any other health scares about which they may have read or heard are without foundation.

References

1. Vessey M, Lawless M, Yeates D. Efficacy of different contraceptive methods. *Lancet* 1982; **1:** 841-842.
2. Schmidt SS. Technics and complications of elective vasectomy: the role of spermatic granuloma in spontaneous recanalization. *Fertil Steril* 1966; **17:** 467-482.
3. Lemack GE, Goldstein M. Presence of sperm in the pre-vasectomy reversal semen analysis: incidence and implications. *J Urol* 1996; **155:** 167-169.
4. Campbell, WB. Vasectomy and arterial disease. *J Roy Soc Med* 1988; **81:** 683-685.
5. Clarkson TB, Alexander NJ. Effect of vasectomy on diet-induced atherosclerosis. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
6. Clarkson TB, Alexander NJ. Long-term vasectomy: effects on the occurrence and extent of atherosclerosis in rhesus monkeys. *J Clin Invest* 1980; **65:** 15-25.
7. Lauersen NH, Muchmore E, Shulman S, *et al.* Vasectomy and atherosclerosis in *Macaca fascicularis:* New findings in a controversial issue. *J Reprod Med* 1983; **28:** 750-758.
8. Clarkson TB, Alexander NJ, Morgan TM. Atherosclerosis of cynomolgous monkeys hyper- and hyporesponsive to dietary cholesterol. Lack of effect of vasectomy. *Arteriosclerosis* 1988; **8:** 488-498.
9. Bansal N, Majumdar S, Ganguly NK, Chakravarti RN. Long term effects of vasectomy on experimental atherosclerosis in rhesus monkeys. *Aust J Exp Biol Med Sci* 1986; **64:** 527-533.
10. Majumdar S, Bhatia ND, Dahiya R, *et al.* Aggravation of experimental atherosclerosis in vasectomized, cholesterol fed rabbits. *Aust J Exp Biol Med Sci* 1985; **63:** 77-83.
11. Bridges FS, Westerfield RC. Effects of vasectomy and exercise upon aortic extensibility, cholesterol deposition, and stainable tissue lipids. *Biol Reprod* 1984; **31:** 296-302.
12. Fahrenbach HB, Alexander NJ, Senner JW, *et al.* Effects of vasectomy on the retinal vasculature of men. *J Androl* 1980; **1:** 299-303.
13. Linnet L, Moller NPH, Bernth-Petersen P, *et al.* No increase in arteriosclerotic retinopathy or activity in tests for circulating immune complexes 5 years after vasectomy. *Fertil Steril* 1982; **37:** 798-806.
14. Campbell WB, Slack RWT, Clifford PC, *et al.* Vasectomy and atherosclerosis: an association in man? *Br J Urol* 1983; **55:** 430-433.
15. Guang-Hua T, Yu-Hui Z, Yue-Min M, *et al.* Vasectomy and health: Cardiovascular and other diseases following vasectomy in Sichuan Province, People's Republic of China. *Int J Epidemiol* 1988; **17:** 608-617.
16. Chi IC, Kong SK, Wilkens LR, *et al.* Vasectomy and cardiovascular deaths in Korean men: a community-based case-control study. *Int J Epidemiol* 1990; **19:** 1113-1115.
17. Giovannucci E, Tosteson TD, Speizer FE, *et al.* A long-term study of mortality in men who have undergone vasectomy. *N Engl J Med* 1992; **326:** 1392-1398.
18. Nienhuis H, Goldacre M, Seagroatt V, *et al.* Incidence of disease after vasectomy: a record linkage retrospective cohort study. *BMJ* 1992; **304:** 743-746.
19. Coulson AH, Crozier R, Massey FJ, *et al.* Health status of American men - a study of post-vasectomy sequelae. *J Clin Epidemiol* 1993; **46:** 857-920.
20. Bansal N, Majumdar S, Chakravarti RN. Frequency and size of atherosclerotic plaques in vasectomized diabetic monkeys. *Int J Fertil* 1986; **31:** 298-304.
21. Bansal N, Majithia N, Majumdar S, Chakravarti RN. Small vessel disease in vasectomized diabetic monkeys: Light microscopic study. *Appl Pathol* 1986; **4:** 219-224.
22. Thornhill JA, Butler M, Fitzpatrick JM. Could vasectomy accelerate testicular cancer? The importance of prevasectomy examination. *Br J Urol* 1987; **59:** 367.
23. Cale ARJ, Farouk M, Prescot RJ, Wallace IWJ. Does vasectomy accelerate testicular tumour? Importance of testicular examinations before and after vasectomy. *BMJ* 1990; **300:** 370.
24. Hewitt G, Logan CJH, Curry RC. Does vasectomy cause testicular cancer? *Br J Urol* 1993; **71:** 607-608.
25. Moller H, Knudsen LB, Lynge E. Risk of testicular cancer after vasectomy: Cohort study of over 73 000 men. *BMJ* 1994; **309:** 295-299.
26. Rosenberg L, Palmer JR, Zauber AG, *et al.* Vasectomy and the risk of prostate cancer. *Am J Epidemiol* 1990; **132:** 1051-1055.
27. Mettlin C, Natarajan N, Huben R. Vasectomy and prostate cancer risk. *Am J Epidemiol* 1990; **132:** 1056-1061.
28. Honda GD, Bernstein L, Ross RK, *et al.* Vasectomy, cigarette smoking, and age at first sexual intercourse as risk factors for prostate cancer in middle-aged men. *Br J Cancer* 1988; **57:** 326-331.
29. Sidney S, Quesenberry CP, Sadler MC, *et al.* Vasectomy and the risk of prostate cancer in a cohort of multiphasic health-checkup examinees: second report. *Cancer Causes Control* 1991; **2:** 113-116.
30. Hayes RB, Pottern LM, Greenberg R, *et al.* Vasectomy and prostate cancer in US blacks and whites. *Am J Epidemiol* 1993; **137:** 263-269.
31. Rosenberg L, Palmer JR, Zauber AG, *et al.* The relation of vasectomy to the risk of cancer. *Am J Epidemiol* 1994; **140:** 431-438.

32. John EM, Whittemore AS, Wu AH, *et al.* Vasectomy and prostate cancer: results from a multiethnic case-control study. *J Nat Cancer Inst* 1995; **87:** 662-669.
33. Giovannucci E, Ascherio A, Rimm EB, *et al.* A prospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993; **269:** 873-877.
34. Giovannucci E, Tosteson TD, Speizer FE, *et al.* A retrospective cohort study of vasectomy and prostate cancer in US men. *JAMA* 1993; **269:** 878-882.
35. Spitz MR, Fueger JJ, Babaian RJ, Newell GR. Vasectomy and the risk of prostate cancer. *Am J Epidemiol* 1991; **134:** 108-109.
36. Giovannucci E. Epidemiologic characteristics of prostate cancer. *Cancer* 1995; **75:** 1766-1777.
37. Guess HA. Is vasectomy a risk factor for prostate cancer? *European J Cancer* 1993; **29A:** 1055-1060.
38. Hsing AW, Wang RT, Gu FL, *et al.* Vasectomy and prostate cancer risk in China. *Cancer Epidemiol Biomarkers and Prevention* 1994; **3:** 285-288.
39. Farley TMM, Meirik O, Mehta S, Waites GMH. The safety of vasectomy: recent concerns. *WHO Bulletin OMS* 1993; **71:** 413-419.
40. Howards SS. Possible biological mechanisms for a relationship between vasectomy and prostate cancer. *European J Cancer* 1993; **29A:** 1060-1062.
41. Scottish Health Statistics. ISD Publications, Common Services Agency, Edinburgh, 1995.
42. Howards SS, Johnson AL. Effects of vasectomy on intratubular hydrostatic pressure in the testis and epididymis. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
43. Bedford JM. Adaptations of the male reproductive tract and the fate of spermatozoa following vasectomy in the rabbit, rhesus monkey, hamster and rat. *Biol Reprod* 1976; **14:** 118-142.
44. Beaton Y, Bennett NK, McDonald SW. Effects of vasectomy on the guinea pig epididymis. *Clin Anat* 1995; **8:** 148.
45. Smith G. The effects of ligation of the vasa efferentia and vasectomy on testicular function in the adult rat. *J Endocrinol* 1962; **23:** 385-399.
46. McDonald SW, Scothorne, RJ. On the response of the regional testicular lymph nodes after unilateral vasectomy in rats. *J Anat* 1986; **144:** 49-59.
47. Pardanani DS, Patil NG, Pawar HN. Some gross observations of the epididymides following vasectomy: a clinical study. *Fertil Steril* 1976; **27:** 267-270.
48. Shapiro EI, Silber SJ. Open-ended vasectomy, sperm granuloma, and post-vasectomy orchialgia. *Fertil Steril* 1979; **32:** 546-550.
49. Errey BB, Edwards IS. Open-ended vasectomy: an assessment. *Fertil Steril* 1986; **45:** 843-846.
50. Lee HY. A 20-year experience with vasovasostomy. *J Urol* 1986; **136:** 413-415.
51. Mullaney J. Granulomatous lesions associated with spermatozoal invasion of the interstitial tissues of the epididymis. *Br J Urol* 1962; **34:** 351-355.
52. Berg JW. An acid-fast lipid from spermatozoa. *AMA Arch Pathol* 1954; **57:** 115-120.
53. Caldwell JC, McGadey J, Kerr R, *et al.* Cell recruitment to the sperm granuloma which follows vasectomy in the rat. *Clin Anat* 1996; **9:** 302-308.
54. Lewis J, McDonald SW. Immune response following vasectomy in the rat: a study of the stimulation of the regional lymph node. *J Anat* 1992; **181:** 471-479.
55. Samuel T, Kolk AHJ, Rumke P, Van Lis JMJ. Auto-immunity to sperm antigens in vasectomized men. *Clin Exp Immunol* 1975; **21:** 65-74.
56. Ansbacher R, Hodge P, Williams A, Mumford DM. Vas ligation: humoral sperm antibodies. *Int J Fertil* 1976; **21:** 258-260.
57. Fawcett DW. Interpretation of the sequelae of vasectomy. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
58. McDonald SW, Halliday J. Cell-mediated immune response after vasectomy in rats. *J Reprod Fertil* 1992; **96:** 529-535.
59. Jessop TS, Ladds PW. The immunopathology of unilateral vasectomy in the ram. *Vet Immunol Immunopathol* 1995; **47:** 123-133.
60. Hooper P, Smythe E, Richards RC, *et al.* Total number of immunocompetent cells in the normal rat epididymis and after vasectomy. *J Reprod Fertil* 1995; **104:** 193-198.
61. Sutherland PD, Matson PL, Masters JRW, Pryor JP. Association between infertility following reversal of vasectomy and the presence of sperm agglutinating activity in semen. *Int J Androl* 1984; **7:** 503-508.
62. Hendry WF, Hughes L, Scammel G, *et al.* Comparison of prednisolone and placebo in subfertile men with antibodies to spermatozoa. *Lancet* 1990; **335:** 85-88.
63. Belker AM, Thomas AJ, Fuchs EF, *et al.* Results of 1469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. *J Urol* 1991; **145:** 505-511.
64. Belker AM, Oates RD, Goldstein M, *et al.* Results in the United States with sperm microaspiration retrieval techniques and assisted reproductive technologies. *J Urol* 1994; **151:** 1255-1259.
65. Abuzeid MI, Chan MY, Sasy MA, *et al.* Fertilization and pregnancy achieved by intracytoplasmic injection of sperm retrieved from testicular biopsies. *Fertil Steril.* 1995; **64:** 644-646.
66. Craft IL, Khalifa Y, Boulos A, *et al.* Factors influencing the outcome of in-vitro fertilization with percutaneous aspirated epididymal spermatozoa and intracytoplasmic sperm injection in azoospermic men. *Human Reprod* 1995; **10:** 1791-1794.
67. Alexander NJ, Tung KSK. Vasectomy in the rabbit: immunological and morphological effects. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
68. Alexander NJ, Tung KSK. Effects of vasectomy in rhesus monkeys. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
69. Rousseaux-Prevost R, De Almeida M, Jouannet P, *et al.* Auto-antibodies to human sperm basic nuclear proteins in infertile and vasectomized men: characterization of antigens and epitopes recognized by antibodies. *Molecular Immunology* 1992; **29:** 895-902.
70. Adourian U, Shampaine EL, Hirshman CA, *et al.* High-titer protamine-specific IgG antibody associated with anaphylaxis: report of a case and quantitative analysis of antibody in vasectomized men. *Anesthesiology* 1993; **78:** 368-372.
71. Metz S, Hirshman CA. Prior vasectomy and anaphylaxis following protamine: no cause and effect. *Anesthesiol* 1993; **79:** 617-619.
72. Derrick FC, Glover WL, Kanjuparamban Z, *et al.* Histological changes in the seminiferous tubules after vasectomy. *Fertil Steril* 1974; **25:** 649-658.
73. Gupta AS, Kothari LK, Dhruva A, Bapna R. Surgical sterilization by vasectomy and its effect on structure and function of the testis in man, *Br J Surg* 1975; **62:** 59-63.
74. Fallon B, Jacobo E, Bunge RG. Restoration of fertility by vasovasostomy. *J Urol* 1978; **119:** 85-86.
75. Jenkins IL, Muir VY, Blacklock NJ, *et al.* Consequences of vasectomy: an immunological and histological study related to subsequent fertility. *Br J Urol* 1979; **51:** 406-410.
76. Bigazzi PE, Alexander NJ, Silber SS. Studies on testicular biopsies from vasectomized men. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
77. Jarow JP, Budin RE, Dym M, *et al.* Quantitative pathologic changes in the human testis after vasectomy. A controlled study. *N Engl J Med* 1985; **313:** 1252-1256.
78. Mehrotra R, Nath P, Singh KM, *et al.* Changes in seminiferous tubules after vasectomy. *Int J Pathol Microbiol* 1985; **28:** 371-378.
79. Jarow JP, Goluboff ET, Chang TSK, Marshall FF. Relationship between antisperm antibodies and testicular histologic changes in humans after vasectomy. *Urology* 1994; **43:** 521-524.
80. Grewal RS, Sachan MS. Changes in testicle after vasectomy. An experimental study. *Int Surg* 1968; **49:** 460-462.
81. Kothari LK, Mishra P, Mishra RK. Effect of bilateral vasectomy on the structure and function of the testes. *Am J Surg* 1973; **126:** 84-88.
82. Vare AM, Bansal PC. Changes in the canine testis after bilateral vasectomy - an experimental study. *Fertil Steril* 1973; **24:** 793-797.
83. MacDougall MK, McCowin K, Derrick FK, *et al.* The effects of vasectomy on spermatogenesis in the dog, Canis familiaris: a meiotic analysis. *Fertil Steril* 1975; **26:** 786-790.
84. McDonald SW, Lockhart A, Gormal D, Bennett NK. Changes in the testis following vasectomy in the rat. *Clin Anat* 1996; **9:** 296-301.
85. Tung KSK. Pathogenesis of testicular pathology in vasectomized guinea pigs. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
86. Muir V, Turk JL, Hanley HG. Comparison of allergic aspermatogenesis with that induced by vasectomy. I In vivo studies in the guinea pig. *Clin Exp Immunol* 1976; **24:** 72-80.
87. Aitken H, Bennett NK, McDonald SW. Changes in the testis following vasectomy in the guinea pig. *Clin Anat* 1995; **8:** 367.
88. Aitken H, Reid O, Neilson M, McDonald SW. Degeneration of the guinea pig testis following vasectomy. *Clin Anat* 1996; **9:** 193-194.
89. Aitken H, Reid O, Bennett NK, McDonald SW. Cellular infiltration of the guinea pig testis following vasectomy. *Clin Anat* 1996: **9:** 194.
90. Bigazzi PE. Immunopathological findings in vasectomized rabbits. In: Lepow IH, Crozier R (eds). *Vasectomy: immunologic and pathophysiologic effects in animals and man.* New York: Academic Press, 1979.
91. Richards IS, Davis JE, Lubell I. Current status of endocrinologic effects of vasectomy. *Urology* 1981; **18:** 1-6.

92. Petty R. Serum testosterone, vasectomy and erectile dysfunction: a study. In: *The Royal College of General Practitioners Members' Reference Book 1994.* London: Royal College of General Practitioners, 1994.
93. Carruthers M. *Vasectomy, the viropause and male hormone replacement therapy.* Report from Positive Health Centre. London: Positive Health Centre, 1991.
94. Buchholz NP, Weuste R, Mattarelli G, *et al.* Post-vasectomy erectile dysfunction. *J Psychosom Res* 1994; **38:** 759-762.
95. McDonald SW. Vasectomy: sequelae in the human epididymis and ductus deferens: a review. *Clin Anat* 1996; **9:** 337-342.
96. Silber SJ. Epididymal extravasation following vasectomy as a cause for failure of vasectomy reversal. *Fertil Steril* 1979; **31:** 309-315.
97. Jarvis LJ, Dubbins PA. Changes in the epididymis after vasectomy: sonographic findings. *Am J Roentgen* 1989; **152:** 531-534.
98. McMahon AJ, Buckley J, Taylor A, *et al.* 1992 Chronic testicular pain following vasectomy. *Br J Urol* 1992; **69:** 188-191.
99. Silber SJ. Sperm granuloma and the reversibility of vasectomy. *Lancet* 1977; **2:** 588-589.
100. McDonald SW, McGrory S, Sim I, Bennett NK. Leakage of spermatozoa from the epididymal duct following vasectomy in the rat. *Clin Anat* 1994; **7:** 56.
101. Phadke AM. Fate of spermatozoa in cases of obstructive azoospermia and after ligation of vas deferens in man. *J Reprod Fertil* 1964; **7:** 1-12.
102. Ball RY, Mitchinson MJ. Obstructive lesions of the genital tract in men. *J Reprod Fertil* 1984; **70:** 667- 673.
103. Barnes MN, Blandy, JP, England HR, *et al.* One thousand vasectomies. *BMJ* 1973; **4:** 216-221.
104. Tailly G, Vereecken RL, Verduyn H. A review of 357 bilateral vasectomies for male sterilization. *Fertil Steril* 1984; **41:** 424-427.
105. Alderman PM. Complications in a series of 1224 vasectomies. *J Fam Pract* 1991; **33:** 579-584.
106. Gould RS. Vasectomy - discomfort and complications in 1100 patients studied: the role of steroids in the prevention of swelling and discomfort. *J Urol* 1974; **112:** 224-225.
107. Manson AL. Trial of ibuprofen to prevent post-vasectomy complications. *J Urol* 1988; **139:** 965-966.
108. Moss WM. A comparison of open-end versus closed-end vasectomies: a report of 6220 cases. *Contraception* 1992; **46:** 521-525.
109. Schmidt SS. Spermatic granuloma: an often painful lesion. *Fertil Steril* 1979; **31:** 178-181.
110. Chen T F, Ball RY. Epididymectomy for post-vasectomy pain: histological review. *Br J Urol* 1991; **68:** 407-413.
111. Pfenninger JL. Complications of vasectomy. *Am Fam Physician* 1984; **30:** 111-115.
112. Raspa RF. Complications of vasectomy. *Am Fam Physician* 1993; **48:** 1264-1268.
113. Selikowitz SM, Schned AR. A late post-vasectomy syndrome. *J Urol* 1985; **134:** 494-497.

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