NEURO-OPHTHALMOLOGY
2017, VOL. 41, NO. 4, 192–197
https://doi.org/10.1080/01658107.2017.1304425

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

An Estimation of the Risk of Pseudotumor Cerebri among Users of the Levonorgestrel Intrauterine Device

Reuben M. Valenzuela[a,b], Ruju Rai[a], Brian H. Kirk[a], Jessica N. Sanders[c], Subhashree Sundar[d], Steffen Hamann[e], Judith E. A. Warner[a,b], Kathleen B. Digre[a,b], Alison V. Crum[a,b], Kirtly P. Jones[c], and Bradley J. Katz[a,b]

[a]Department of Ophthalmology and Visual Sciences; John A. Moran Eye Center, University of Utah Health Sciences Center, Salt Lake City, Utah, USA; [b]Department of Neurology, University of Utah Health Sciences Center, Salt Lake City, Utah, USA; [c]Department of Obstetrics and Gynecology, University of Utah Health Sciences Center, Salt Lake City, Utah, USA; [d]Department of Operations and Information Systems, David Eccles School of Business, University of Utah, Salt Lake City, Utah, USA; [e]Department of Ophthalmology, Rigshospitalet, University of Copenhagen, Glostrup, Denmark

ABSTRACT

Because of a previous association of pseudotumor cerebri (PTC) with levonorgestrel, we wished to evaluate the use of levonorgestrel-eluting intrauterine devices ("levonorgestrel intrauterine systems", LNG-IUS) in our University of Utah and Rigshospitalet PTC patients. In our retrospective series, PTC prevalence was approximately 0.18% and 0.15% in the LNG-IUS population versus 0.02% and 0.04% in the non-LNG-IUS population (Utah and Rigshospitalet, respectively), with no significant differences in PTC signs and symptoms among the two groups. Our investigation suggests that women with an LNG-IUS may have increased risk of developing PTC but does not suggest an LNG-IUS can cause PTC.

ARTICLE HISTORY
Received 19 February 2017
Received 5 March 2017
Accepted 5 March 2017

KEYWORDS
Contraception; idiopathic intracranial hypertension; intrauterine system; levonorgestrel; pseudotumor cerebri

Introduction

Pseudotumor cerebri is a disorder seen in obese women of childbearing age. It causes increased intracranial pressure without a mass lesion.[1] The morbidity of the disorder includes visual loss from papilloedema, headaches, and reduced quality of life.[2,3] There is an idiopathic form (idiopathic intracranial hypertension), but a number of medications have been associated with the secondary form, pseudotumor cerebri syndrome, including tetracycline and minocycline. The development of the condition is often associated with weight gain.[1,2,4,5]

In 1995, Alder, Fraunfelder, and Edwards described eight women with pseudotumor cerebri (PTC) who had received levonorgestrel contraceptive implants (Norplant®).[6] The authors could not confirm a causative role for this contraceptive device but speculated that it could cause elevated intracranial pressure through changes in fat metabolism, vitamin A metabolism, or venous microthrombi. An intrauterine device that releases levonorgestrel is referred to as a levonorgestrel intrauterine system (LNG-IUS). An LNG-IUS may be offered to women who have contraceptive challenges such as obesity, migraine or other headaches, or polycystic ovary syndrome, as well as those with contraindications to oestrogen.[7] The US Food and Drug Administration (FDA) approved Mirena® as a contraceptive device in 2000. This LNG-IUS releases levonorgestrel at approximately 20 μg/day. Another LNG-IUS that releases levonorgestrel, at a lower rate of approximately 6 μg/day, was approved for use in Europe in 2012 under the trade name Jaydess® and for use in the United States in 2013 under the trade name Skyla®. In 2015, the FDA approved a second LNG-IUS (Liletta®) that releases levonorgestrel at 18.6 μg/day.

Because of the previously documented association of PTC with Norplant®, we wished to determine if any of our PTC patients from the University of Utah Health Sciences Center (USA) and the Rigshospitalet (Denmark) were using an LNG-IUS, if use of an LNG-IUS was associated

CONTACT Bradley J. Katz, MD, PhD Bradley.katz@hsc.utah.edu Department of Ophthalmology and Visual Sciences; John A Moran Eye Center, 65 N Mario Capecchi Drive, Salt Lake City, UT 84132, USA.

Drs. Valenzuela and Rai contributed equally to the work and are co-first authors.

with an increased risk of PTC, and if PTC patients with an LNG-IUS had signs or symptoms that were different from those observed in PTC patients without an LNG-IUS.

Materials and methods

University of Utah

This study was approved by the University of Utah Institutional Review Board (IRB). We identified patients from the University of Utah's PTC database. This database includes all patients with PTC seen by one of the authors (J.E.A.W., K.B.D., A.V. C., B.J.K.) between 2003 and 2013. Inclusion criteria included females with a PTC diagnosis, aged 18–55, and between 2008 and 2013. Patients diagnosed with PTC prior to this time period (i.e., recurrent cases) were excluded. We only included women for whom we could obtain a birth control history during the 3 months preceding the onset of symptoms attributable to increased intracranial pressure. First, an introductory letter was mailed to potential participants. A telephone interview was conducted to confirm clinical and birth control histories. Presenting patient characteristics and clinical signs and symptoms were extracted from the PTC database for analysis.

Next, we identified all women in the University of Utah Electronic Billing database who had been billed for LNG-IUS insertion between 2008 and 2013, using the Current Procedural Terminology (CPT) code 58300/J7302. We excluded women who had a concurrent International Classification of Diseases Ninth Revision (ICD-9) code for PTC. We only included women aged 18–55, with at least one clinical encounter from 2008 to 2013.

Rigshospitalet

The review of Rigshospitalet patient files was approved by the Danish Health and Medicines Authority. We reviewed cases that we identified in Glostrup Hospital (now called Rigshospitalet) files, and in the Department of Ophthalmology's idiopathic intracranial hypertension (IIH) database. This database includes all patients with PTC seen at the department from 2007 to 2014. Inclusion criteria included females with a PTC diagnosis at ages 18–55 years, and between 2008 and 2014. Recurrent cases were excluded. Only women for whom we could obtain a birth control history during the 3 months preceding the onset of symptoms attributable to increased intracranial pressure were included.

Next, we identified all women in the same age group with at least one clinical encounter at Rigshospitalet from 2008 to 2014, and how many of those women received a diagnosis of PTC. Presenting clinical characteristics and other symptoms and signs were extracted from the records for analysis.

Statistical analyses

We used bivariate analysis (*t* test for continuous variables and Pearson's chi-square for categorical variables) to compare the basic characteristics of PTC patients who had LNG-IUS exposure with those patients who were using other forms of contraception or no contraception. Crude associations (unadjusted) were examined for LNG-IUS exposure to examine relative risk, excess risk, attributable risk, and odds ratios. We addressed the issue of multiplicity by applying the Hochberg procedure to adjust for multiple comparisons.[8,9] Statistical analysis was carried out using Stata, version 13.0 (College Station, TX, USA) and Excel 2011 (Microsoft Corp., Redmond, WA, USA).

Results

University of Utah

The University of Utah PTC database contains 473 patients. Of these, 176 patients met inclusion criteria and were sent introductory letters. We were able to complete telephone interviews with 59 of these patients. Among these 59 women, 8 (14%) confirmed that they had an LNG-IUS in place at the time of the onset of PTC symptoms. Of the 59 women completed the interview, 9 (15%) were using another contraceptive and 42 (71%) were not using any contraceptives within 90 days of the onset of symptoms.

All 8 women with an LNG-IUS developed symptoms of PTC while the device was still in situ. The mean duration of exposure to LNG-IUS prior to symptom onset in this group was 22

months (range: 1 month to 5 years). We found no significant difference in the perimetric mean deviation in the worse-seeing eye or in any of the other symptoms or signs of the 8 patients with an LNG-IUS and the 51 patients without an LNG-IUS (Table 1).

From the University of Utah Electronic Billing database, we identified 220,904 women without PTC; 4408 of these women underwent LNG-IUS insertion between 2008 and 2013.

The prevalence of PTC was approximately 0.18% in the LNG-IUS population (8/4408, 95% confidence interval [CI]: 0.07%–0.35%) versus 0.02% in the non–LNG-IUS population (51/[220,904 + 59 − 4408]; 95% CI: 0.01%–0.03%). In a crude analysis of the aggregate data, the excess risk (or attributable risk) observed in the LNG-IUS group was 0.15% (95% CI: 0.03%–0.20%), and the relative risk for the LNG-IUS group was 7.69 (95% CI: 3.65–16.19). The unadjusted odds ratio indicated that exposure to LNG-IUS was associated with increased odds of PTC diagnosis of 7.70 (95% CI: 3.7–16.0).

Table 1. Presenting clinical features of women with pseudotumor cerebri with and without a levonorgestrel intrauterine system (LNG-IUS) at the University of Utah.

Characteristic	+LNG-IUS (n = 8)	−LNG-IUS (n = 51)	p value
Presenting characteristics			
Mean age (SD)	30 (6)	32 (9)	0.62
Mean body mass index (BMI) (SD)	35 (9)	35 (7)	0.92
Recent weight gain, *n* (%)	4 (50)	13 (25)	0.16
Migraine history, *n* (%)	3 (38)	20 (39)	0.93
Presenting symptoms			
Headaches, *n* (%)	5 (63)	44 (86)	0.10
Pulsatile tinnitus, *n* (%)	4 (50)	29 (57)	0.71
Transient visual obscurations, *n* (%)	3 (38)	22 (43)	0.68
Blurred vision, *n* (%)	3 (38)	19 (37)	0.99
Nausea, *n* (%)	1 (13)	14 (28)	0.37
Presenting signs			
Mean LogMAR BCVA (SD)			
Worse eye	0.06 (0.11)	0.09 (0.30)	0.81
Fellow eye	−0.01 (0.10)	0.05 (0.29)	0.56
Difference between eyes	0.08 (0.09)	0.04 (0.11)	0.42
Mean perimetric deviation db (SD)			
Worse eye	−5.6 (5.5)	−6.2 (7.5)	0.81
Fellow eye	−2.9 (3.1)	−4.1 (5.4)	0.56
Difference between eyes	−2.7 (2.7)	−1.8 (3.0)	0.42
Frisén papilloedema stage*, *n* (%)	*n* = 7	*n* = 50	
Worse eye			0.19
Stages 0–1	1 (13)	17 (34)	
Stages 2–3	5 (63)	22 (44)	
Stages 4–5	1 (13)	11 (22)	
Fellow eye			0.55
Stages 0–1	2 (25)	23 (46)	
Stages 2–3	4 (50)	18 (36)	
Stages 4–5	1 (13)	9 (18)	

Note. We analysed the pre-existing characteristics, signs, and symptoms among 59 women with pseudotumor cerebri. Eight women had an LNG-IUS (+LNG-IUS) when they first experienced symptoms of elevated intracranial pressure, and 51 women did not have an LNG-IUS (−LNG-IUS) at symptom onset. For the conditions, signs, and symptoms analysed, there were no significant differences between these two groups.

*We were unable to obtain Frisén papilloedema grade for one woman with an LNG-IUS and one woman without an LNG-IUS.

Rigshospitalet

The Glostrup Hospital Department of Ophthalmology IIH database contains 92 patients. Of these, 64 patients met inclusion criteria, and the files of all 64 patients were reviewed. Eight (13%) had an LNG-IUS in place at the time of onset of PTC symptoms, 8 (13%) were using another contraceptive, and 48 (75%) were not using any contraceptives.

All 8 women with an LNG-IUS developed symptoms of PTC while the device was still in situ. We found no significant difference in perimetric mean deviation in the worse-seeing eye when comparing the patients with or without an LNG-IUS. When comparing the other symptoms and signs in these two groups, the only significant difference we identified was perimetric mean deviation in the better-seeing eye; however, once we adjusted for multiple comparisons, this finding was no longer significant (Table 2).

During the period from 2008 to 2014, we identified 154,877 women in the age group 18–55 who visited Glostrup Hospital at least once and who did not have PTC. In 2014, 47,300 LNG-IUS were sold in Denmark (Bayer HealthCare Pharmaceuticals Inc., personal communication). In Denmark, LNG-IUS are prescribed only to women aged 15–49. There are approximately 1,340,000 Danish women in this age group (Statistics Denmark; https://www.dst.dk/en). These statistics indicate that approximately 3.5% of Danish women of childbearing age (47,300/1,340,000) have an LNG-IUS at any given time. With 3.5% of women having an LNG-IUS, an estimated 5467 women underwent LNG-IUS insertion at Glostrup hospital between 2008 and 2014.

The prevalence of PTC was approximately 0.15% in the LNG-IUS population (8/5467)

Table 2. Presenting clinical features of women with pseudotumor cerebri with and without a levonorgestrel intrauterine system (LNG-IUS) at Rigshospitalet.

Characteristic	+LNG-IUS (n = 8)	–LNG-IUS (n = 56)	p value
Presenting characteristics			
Mean age (SD)	29 (4)	28 (8)	0.56
Mean body mass index (BMI) (SD)	36 (5)	37 (7)	0.65
Recent weight gain, *n* (%)	1 (13)	13 (23)	0.67
Migraine history, *n* (%)	3 (38)	5 (9)	0.05
Presenting symptoms			
Headaches, *n* (%)	8 (100)	55 (98)	1.00
Pulsatile tinnitus, *n* (%)	6 (75)	28 (50)	0.26
Transient visual obscurations, *n* (%)	3 (38)	28 (56)	0.71
Blurred vision, *n* (%)	5 (63)	42 (75)	0.67
Nausea, *n* (%)	2 (25)	26 (46)	0.45
Presenting signs			
Mean LogMAR BCVA (SD)			
Worse eye	0.07 (0.15)	0.09 (0.28)	0.78
Fellow eye	−0.05 (0.05)	0.00 (0.14)	0.11
Difference between eyes	0.11 (0.13)	0.09 (0.19)	0.69
Mean perimetric deviation* db (SD)	n = 7	n = 42	0.05
Worse eye	−3.1 (2.1)	−5.7 (5.6)	0.02
Fellow eye	−2.0 (1.2)	−4.2 (5.0)	0.53
Difference between eyes	−1.1 (1.1)	−1.5 (1.9)	
Frisén papilloedema stage†, *n* (%)	n = 8	n = 48	
Worse eye			0.35
Stages 0–1	3 (38)	9 (19)	
Stages 2–3	4 (50)	23 (48)	
Stages 4–5	1 (13)	16 (33)	
Fellow eye			0.85
Stages 0–1	4 (50)	23 (48)	
Stages 2–3	3 (38)	15 (31)	
Stages 4–5	1 (13)	10 (21)	

Note. We analysed the pre-existing characteristics, signs, and symptoms among 64 women with pseudotumor cerebri. Eight women had an LNG-IUS (+LNG-IUS) when they first experienced symptoms of elevated intracranial pressure, and 56 women did not have an LNG-IUS (–LNG-IUS) at symptom onset. For the conditions, signs, and symptoms analysed, there were no significant differences between these two groups.

*We were unable to obtain mean perimetric deviation in one woman with an LNG-IUS and 14 women without an LNG-IUS.

†We were unable to obtain Frisén papilloedema grade for 8 women without an LNG-IUS.

versus 0.04% in the non–LNG-IUS population (56/[154,877 + 64 − 5467]). In a crude analysis of the aggregate data, the excess risk (or attributable risk) observed in the LNG-IUS group was 0.11% (95% CI: 0.01%–0.21%), and the relative risk for the LNG-IUS group was 3.90 (95% CI: 1.86–8.18). The unadjusted odds ratio indicated that exposure to LNG-IUS was associated with increased odds of PTC diagnosis of 3.91(95% CI: 1.89–8.06).

Discussion

When comparing the signs and symptoms of the PTC patients with and without an LNG-IUS, the only difference we found was in the perimetric mean deviation of the less affected eye in the Danish group. However, because we made multiple comparisons in our secondary outcome, this difference may have occurred by chance and was no longer statistically significant when we applied the Hochberg procedure. Otherwise, the signs and symptoms of the subjects with PTC and with an LNG-IUS were not significantly different from those documented in the subjects with PTC and without an LNG-IUS. This result indicates that if an LNG-IUS is somehow associated with the development of PTC, it does not cause a form of PTC that can be distinguished from IIH based on clinical signs, clinical symptoms, or lumbar puncture opening pressure.

Our investigation suggests that women with an LNG-IUS may have an increased risk of developing PTC. Our investigation does *not* indicate that an LNG-IUS can cause PTC, and the number of women with an LNG-IUS was too small to determine if an LNG-IUS is an *independent* risk factor for PTC. Although use of an LNG-IUS seems be associated with an increased risk of PTC, it is possible that this observation occurred because use of an LNG-IUS is also associated with other established risk factors that are known to be associated with PTC (e.g., obesity and recent weight gain). The analysis was also limited by the lack of temporal data to confirm that exposure to LNG-IUS occurred prior to PTC symptom onset or diagnosis.

Previous reports on another LNG contraceptive implant, Norplant®, suggested an association with PTC.[6,10,11] As in the present report, these previous reports did not imply a causative role for LNG in the pathogenesis of PTC. It has been hypothesised that LNG could cause increased intracranial pressure through a number of mechanisms, including vitamin A metabolism or venous microthrombi, mechanisms that have both been previously proposed as causes of PTC.[12] It is unclear why LNG would cause this syndrome but other progestins used for birth control would not. It is also unclear why exogenous LNG would cause this syndrome

but endogenous progestins (such as those associated with pregnancy) would not cause this syndrome.

There are two possible explanations for the association demonstrated in our study. One explanation is that LNG does cause increased intracranial pressure, either through one of the mechanisms discussed above or through another, as yet unknown mechanism. Another explanation is that LNG does not cause increased intracranial pressure, but that PTC is more likely to occur in the same population of women who are more likely to have an LNG-IUS recommended to them by their physician. LNG-IUS is often, although not exclusively, recommended for women who may have difficulty with other forms of contraception. For instance, women with obesity, headache, and/or polycystic ovarian syndrome are more likely to be intolerant to oral contraceptives. For this group of women, an LNG-IUS may be better tolerated as a form of contraception.[7] This same group of women, with obesity, headache, and polycystic ovarian syndrome, are also more likely to develop PTC.[13,14] When interpreting the findings presented here, it is also important to consider that the risk analysis does not account for potential confounders.

Future research may or may not be able to distinguish between these two possibilities. Currently, there are no reliable animal models of PTC. Such a model would allow researchers to determine whether LNG increases intracranial pressure. A prospective trial of LNG-IUS in a population of women at risk for PTC would likely be too costly and would not settle the question of whether an LNG actually causes PTC. A larger, observational case-crossover study that examined potential confounders could be conducted to more reliably estimate the risk of PTC among LNG-IUS users, but such a study would not settle the question of whether an LNG actually causes increased intracranial pressure. This larger study might be able to determine if LNG-IUS is an *independent* risk factor for PTC. A recent observational case-crossover study demonstrated an increased risk of non-arteritic anterior ischaemic optic neuropathy among male users of phosphodiesterase inhibitors.[15] Adequately powering this study of ischaemic optic neuropathy required the participation of more than 100 ophthalmology centres in the United States and Europe.

Strengths of our study include the review of records from two different institutions in two different countries and the observation of similar results. Although there were some differences in the way the data were collected at the two sites, we believe these differences are comparatively minor and do not affect the results or conclusions.

Limitations of our study include the retrospective nature of the investigation and the relatively small number of PTC subjects with an LNG-IUS at the time of diagnosis. It was not possible for the University of Utah group to capture the number of LNG-IUS insertions performed outside of the university system, so we may have underestimated the number of women with an LNG-IUS. It is also possible that some women who did not have an LNG-IUS were taking an oral contraceptive that contained LNG.

Although antibiotic prophylaxis is not recommended for intrauterine device (IUD) insertion,[16] some women are given a course of oral doxycycline following IUD insertion, especially if they experience pelvic pain following insertion.[17] Women may also be given a course of antibiotics at other time points while the IUD is in place for breakthrough bleeding. Tetracycline antibiotics are also a known risk factor for PTC.[14] Antibiotics are not customarily administered to women undergoing IUD insertion at our two institutions, but we did not specifically ask our participants if they recalled being given a course of antibiotics. It is not possible for us to entirely rule out the possibility that any of our LNG-IUS patients received antibiotics at the time of IUD insertion. A course of oral contraceptives may also be given to women with an IUD who are experiencing breakthrough bleeding. Because of these limitations, we have striven to be circumspect about our results, conclusions, and recommendations.

Our findings are preliminary, and caution should be exercised in applying this information to clinical practice. At this time, our recommendation is that physicians caring for patients with PTC obtain a birth control history from all of their PTC patients. Patients with an LNG-IUS may not be aware that this device contains a drug and often will not list the IUD on their medication intake history unless specifically questioned. Women who have an LNG-

IUS should be asked if they received a course of antibiotics at the time of device insertion. We do not recommend the removal of LNG-IUS from women with PTC, as the benefit of effective contraception for these women likely outweighs the risk. Likewise, if a woman with PTC or at risk for PTC needs contraception, an LNG-IUS should still be considered as an effective form of contraception.

Acknowledgements

The Authors thank Ms. Susan Schulman, Links to Clinical Research, for professional editing of the final manuscript.

Declaration of interest

Jessica Sanders receives research funding for other projects from Bayer HealthCare, Whippany, New Jersey, USA, and Teva Women's Health Inc., Frazer, Pennsylvania, USA.

The other authors report no relevant conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York, USA, to the Department of Ophthalmology and Visual Sciences, University of Utah, Salt Lake City, Utah, USA.

References

[1] Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology* 2013;81:1159–1165.

[2] Wall M. Idiopathic intracranial hypertension (pseudotumor cerebri). *Curr Neurol Neurosci Rep* 2008;8:87–93.

[3] Wall M. Update on idiopathic intracranial hypertension. *Neurol Clin* 2017;35:45–57.

[4] Thurtell MJ, Bruce BB, Newman NJ, Biousse V. An update on idiopathic intracranial hypertension. *Rev Neurol Dis* 2010;7:e56–e68.

[5] Chen J, Wall M. Epidemiology and risk factors for idiopathic intracranial hypertension. *Int Ophthalmol Clin* 2014;54:1–11.

[6] Alder JB, Fraunfelder FT, Edwards R. Levonorgestrel implants and intracranial hypertension. *N Engl J Med* 1995;332:1720–1721.

[7] d'Arcangues C. Worldwide use of intrauterine devices for contraception. *Contraception* 2007;75:S2–S7.

[8] Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *BMJ (Clin Res Ed)* 1983;286:1489–1493.

[9] Wright SP. Adjusted P-values for simultaneous inference. *Biometrics* 1992;48:1005–1013.

[10] Wysowski DK, Green L. Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995;85:538–542.

[11] Sivin I. Comment: Serious adverse events in Norplant users reported to the Food and Drug Administration's MedWatch Spontaneous Reporting System. *Obstet Gynecol* 1995;86:318–320

[12] Friedman DI, Jacobson DM. Idiopathic intracranial hypertension. *J Neuroophthalmol* 2004;24:138–145.

[13] Daniels AB, Liu GT, Volpe NJ, Galetta SL, Moster ML, Newman NJ, Biousse V, Lee AG, Wall M, Kardon R, Acierno MD, Corbett JJ, Maguire MG, Balcer LJ. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol* 2007;143:635–641.

[14] Glueck CJ, Aregawi D, Goldenberg N, Golnik KC, Sieve L, Wang P. Idiopathic intracranial hypertension, polycystic-ovary syndrome, and thrombophilia. *J Lab Clin Med* 2005;145:72–82.

[15] Campbell UB, Walker AM, Gaffney M, Petronis KR, Creanga D, Quinn S, Klein BE, Laties AM, Lewis M, Sharlip ID, Kolitsopoulos F, Klee BJ, Mo J, Reynolds RF. Acute nonarteritic anterior ischemic optic neuropathy and exposure to phosphodiesterase type 5 inhibitors. *J Sex Med* 2015;12:139–151.

[16] ACOG Practice Bulletin No. 121: Long-acting reversible contraception: implants and intrauterine devices. *Obstet Gynecol* 2011;118:184–196.

[17] Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion*Cochrane Database Syst Rev* 2001;(2):CD001327.