SURGICAL PROPHYLAXIS

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Surgical prophylaxis is usually considered to be of value in operations involving clean-contaminated wounds e.g. abdominal and vaginal hysterectomy. Recent evidence is accumulating also on the possible benefit of chemoprophylaxis for first trimester abortions.

In pathogenesis of post-operative wound infections involving clean-contamined wounds, the following factors are important:

1. the number of organisms introduced into the wound
2. their virulence.
3. the presence of tissue fluids which serve them as a culture medium
4. the host's inherent resistance to infection.

The rationale of chemoprophylaxis is that the antibiotics available during the operation should reduce the number of organisms and also render the tissue fluid less suitable as a culture medium. It is important to stress here that the most effective measure in the prevention of post-operative wound infection is the meticulous care taken by the surgeon at operation.

HYSTERECTOMIES

Many studies, including several reviews, have been published in the past decade on the efficacy of chemoprophylaxis in hysterectomies, but the number of randomized clinical trials is small (Berger *et al.*, 1980; Hirschmann and Inui, 1980; Polk, 1981; Hamod *et al.*, 1982). Polk (1981) presented a synthesis of the results since 1960 of scientifically evaluable reports where the duration of prophylaxis was no longer than 48 hours. The author concentrated on infection at operation sites.

This paper includes work published since the review of Polk and will discuss other aspects of chemoprophylaxis in the light of more recent publications. Results are included only if the study was randomized, double-blind, placebo-controlled or comparative, and with duration of prophylaxis no longer than 48 hours in the peri-operative period.

Vaginal hysterectomy

12 clinical trials of antimicrobial prophylaxis in patients undergoing elective vaginal hysterectomy have been published since 1973 (table 1). Only 2 of the 12 studies fulfilling the criteria for inclusion were carried out in the United Kingdom. The most common infectious complications reported included febrile morbidity, pelvic infection and urinary tract infection. Of these, pelvic infection is the most serious complication for the patient. It represents also an important cause of post-operative fever. Although the detailed definitions of febrile morbidity and pelvic infection may vary from study to study, there is a significant reduction in the

TABLE 1. — *Results of 12 placebo-controlled randomised clinical trials of chemoprophylaxis in vaginal hysterectomy.*

1st Author (year)	Antimicrobial and dosage	Total no. of patients	Pelvic infection (%) Rx	Pelvic infection (%) P	Fever (%) Rx	Fever (%) P	UTI (%) Rx	UTI (%) P
Ledger (1973)	cephaloridine 1 g × 3	100	8	34 *	24	46 *	18	28
Breenden (1974)	cephaloridine 1 g × 3	120	3	20 *	9	52 *	2	7
Holman (1978)	cefazolin 0.5 g × 3	84	0	25 *	5	33 *	10	11
Roberts (1978)	carbenicillin 2 g × 5	52	0	12 *	8	35 *	8	23
Mendelson (1979)	cephradine (1) 1 g × 1 (2) 1 g + 0.5 g × 8	66	2	54 *	5	73 *	37	62
Grossman (1979)	penicillin 1 m.u. × 8 cefazolin 0.59 × 8	78	6	25 *	19	71 *	33	45
Matthews (1979)	sulphamethoxazole 800 g + trimethoprim 160 mg	50	8	16	32	64	20	56
Polk (1980)	cefazolin 1 g × 3	86	2	21 *	14	31 *	23	21
Hemsell (1980)	cefoxitin 2 g × 3	99	8	57 *	14	14	8	2
Mickal (1980)	cefoxitin 2 g × 3	125	10	30 *	—	—	—	—
Stage (1982)	cephradine 1 g × 2	163	2	14 *	12	27 *	8	7
Houang (1984)	ampicillin 0.5 g + sulbactam or metronidazole 1 g × 1	18	8	30 *	0	30 *	10	20

* $p < 0.05$ Treatment vs placebo

incidences of both complications in the treated groups in 11/12 studies reported. There is a wide variation in the rates of pelvic infection in the placebo-treated groups (12-57%). The discrepancies may be related to the well recognized difficulty in both defining and diagnosing pelvic infection after hysterectomy. Febrile morbidity was also uniformly and significantly reduced in all treated groups except those of Hemsell *et al.* (1980). They also reported the lowest incidence of febrile morbidity in a placebo group (14%), compared with an average of 44 per cent in the other studies.

There is only one report which records a significant reduction in urinary tract infection (UTI) in those receiving antibiotics (Matthews *et al.*, 1979); the antibiotic used was a single peri-operative dose of cotrimoxazole. However, urinary tract infection has been shown to be closely related to the duration of catheterization. Polk *et al.* (1980) reported no UTI in the placebo group after straightforward

hysterectomy when the median duration of catheterizations was one day, whereas UTI occurred in 35% of the placebo group of patients undergoing hysterectomy with repair who required a median of six days catheterisation. An increasing incidence of UTI with prolonged catheterisation has been well documented in many studies (Garibaldi *et al.*, 1974). Matthews *et al.* (1979) did not provide details of catheterisation for the fifty patients he studied. The apparent advantage of co-trimoxazole needs, therefore, to confirmed by other studies.

The benefit of chemoprophylaxis is further substantiated by the significant reduction shown in subsequent use of antibiotics (Ledger *et al.*, 1973; Polk *et al.*, 1980; Stage *et al.*, 1982) and the duration of hospital stay (Holman *et al.*, 1978; Mendelson *et al.*, 1979; Hemsell *et al.*, 1980; Polk *et al.*, 1980). In conclusion, short term peri-operative chemoprophylaxis has been shown to be of great value in vaginal hysterectomy. The evidence is strong enough for some authors e.g. Hirchmann and Inui (1980); Polk (1981) to hold that further placebo-controlled trials are not necessary.

The choice of antibiotic for use in vaginal hystrectomy is however more difficult. The vaginal flora consist of a variety of bacterial species, particularly anaerobes (Bartlett *et al.*, 1977). *Bacteroides fragilis* is one of the most important species isolated from patients with post-operative sepsis (Thadepalli *et al.*, 1973). A number of antibiotics have been used (table 1) varying between those with a narrow spectrum of activity e.g. penicillin, to those with broad spectrum activity e.g. cefoxitin. Of the 11 studies reporting a significant reduction in pelvic infection, only 3 employed agents which have high activity against *Bacteroides fragilis in vitro* (Hemsell *et al.*, 1980; Mikal *et al.*, 1980; Houang *et al.*, 1984). This raises the question of whether it is necessary to use antibiotics active against the many different bacterial species in the vagina to achieve effective chemoprophylaxis. As, in placebo-controlled studies, the use of antibiotics with activity against part of the flora e.g. aerobic or anaerobic organisms, leads to signficant reduction in the most serious post-operative complication, namely, pelvic infection, it would seem that it is not.

Abdominal hysterectomy

There are 9 studies which were designed to be placebo-controlled and randomised trials in abdominal hysterectomy (table 2). Four reports show a significant reduction in wound/pelvic infection when prophylactic antibiotics are administered, although it is seen only in studies in which the wound/pelvic infection rate in the placebo-treated group is relatively high (15%). Using the method of synthesis of Polk (1981) it can be demonstrated that the results among the 9 studies are consistent, and the overall reduction is statistically significant. 4 studies showed a significant reduction in the post-operative UTI. They were all associated with a very short duration of catheterisation of about 1½ days (Matthews and Ross, 1977; Holman *et al.*, 1978; Polk *et al.*, 1980). 3 studies (Holman *et al.*, 1978; Roberts and Homesly, 1978; Polk *et al.*, 1980), also showed significant reduction in the duration of hospital stay related to the use of chemoprophylaxis.

TABLE 2. — *Results of placebo-controlled randomised clinical trials of chemoprophylaxis in abdominal hysterectomy.*

1st Author (year)	Antimicrobial and dosage	Total no. of patients	Wound infection (%) Rx	P	Fever (%) Rx	P	UTI (%) Rx	P
Matthews (1977)	cotrimoxazole 1 g × 1	59	27	38	40	40	2	31 *
Holman (1978)	cefazolin 0.5 g × 3	80	5	34 *	14	45 *	2	29 *
Roberts (1978)	carbenicillin 2 g × 5	47	4	14	4	54 *	0	32 *
Grossman (1979)	penicillin 1 m.u. × 8	239	5	11	32	26	11	19
	cefazolin 0.5 g × 8		11	11	35	26	11	19
Polk (1980)	cefazolin 1 g × 3	429	14	21 *	14	20 *	9	21 *
Schepers (1981)	cefoxitin 1 g × 2	103	6	16 *	not available			
Stage (1982)	cephradine 1 g × 2	110	2	5	24	24	5	10
Walker (1982)	metronidazole vag. pessary 1 g × 1	88	13	14	duration of pyrexia (hour) 8.3	15.4	17	12
Houang (1984)	ampicillin 0.5 g and sulbactam or metronidazole P 1 g	158	3.5	24 *	2	20 *	12	14

* Treatment vs placebo $p < 0.05$

After Polk (1981): χ^2 total (12) = 36.37; $p < 0.05$
χ^2 homog. (11) = 13.76; $p > 0.2$
χ^2 assoc. (1) = 22.8; $p < 0.005$

From this review, it is apparent that the use of chemoprophylaxis is more controversial in abdominal than vaginal hysterectomy. Significant reduction, in sepsis, is seen mainly in centres with an intrinsically high infection rate. In other centres, chemoprophylaxis reduces significantly only febrile morbidity and/or UTI. It is generally agreed that routine chemoprophylaxis is only of value if it reduces significantly severe post-operative sepsis, as the benefit has to be balanced against cost and harmful side-effects to the patient and her environment. Febrile morbidity may be related directly to the wound/pelvic infection but also to infection at other sites, which are generally minor and often do not warrant treatment.

Nevertheless, in the author's view the following benefits can be demonstrated. Firstly, UTI represents an important cause of discomfort in many post-operative patients. A chemoprophylactic regimen which can significantly reduce the incidence of post-operative UTI is, therefore, of value. Post-operative urinary tract infection is closely associated with the technique and duration of catheterisation. Unlike vaginal hysterectomy and repair, patients for abdominal hysterectomy, as a rule,

require only short-term catheterisation (<1 day) and short course peri-operative antibiotic may be effective. The antibiotics which are active against the common urinary pathogens are likely to be more effective than those that are not but this premise should be substantiated by clinical trial. Jandial *et al.* (1983) used single dose cefuroxime in a prospective, randomised, but not placebo-controlled study of 472 hysterectomies and showed a significant reduction in post-operative UTI in the group, and, as a result, significant reduction in the number of patients who received post-operative antibiotics.

A second justifiable benefit of chemoprophylaxis in abdominal hysterectomy is if a significant reduction in the total quantity of antibiotics (including that used for chemoprophylaxis) can be demonstrated in the group receiving chemoprophylaxis compared with the placebo group. Apart from the obvious saving, it is also of benefit to the patient and the hospital environment as it imposes less selective pressure for antimicrobial resistance. Such a reduction in the overall usage of antimicrobials is more likely to be achieved if short-course prophylaxis is used. A single dose of antibiotics administered peri-operatively has been shown be as effective as multiple doses (Lett *et al.*, 1977; Mendelson *et al.*, 1979; Hamod *et al.*, 1980). The duration of surgery and the general resistance of the patient are important factors in determining wound infection rates. The efficacy of chemoprophylaxis in reducing infection varies with the time taken for operation: at I hour there is 80% efficacy, diminishing to an unmeasurable level at 3.3 hours. Longer courses of therapy may not enhance the efficacy of prophylaxis and may, in theory at least, increase the risk of drug-related side effects and the emergence of resistant organisms (Duff and Park, 1980).

The antibiotics of choice for prophylaxis of patients before abdominal hysterectomy its not known. The same antibiotic has been found to be effective in one study but not in others. For example, cefazolin (3-8 doses) was shown to reduce significantly wound infection, febrile morbidity and UTI by Holman *et al.* (1978) and Polk *et al.* (1980), whereas Grossman *et al.* (1979), found no significant benefit studying a group with a low wound infection rate (11%). Other antibiotics which have been shown to be effective chemoprophylactic agents in vaginal hysterectomy e.g. carbenicillin, cephradine, have not been so found in abdominal operations. This emphasises the importance of carrying out controlled studies at one's own centre in order to ascertain the efficacy of a particular chemoprophylactic regimen (Gifford and Feinstein, 1969).

Polk (1981) compared results obtained in studies which included both types of hysterectomy and calculated the preventive figure for wound infection in vaginal and abdominal operations to be 90 per cent and 50 per cent respectively. Shapiro *et al.* (1982) calculated the ratio for infection at operation sites after abdominal hysterectomy to be 2.53 when compared with vaginal operation. Holman *et al.* (1978) noted that the operation time for abdominal hysterectomy was approximately one hour longer than that for vaginal hysterectomy. More of the patients having abdominal hysterectomy required transfusions and their mean age was almost ten years greater than that of patients having vaginal hysterectomy.

In comparing the efficacy of two different regimens of antimicrobial agent in reducing infection following hysterectomy, it is important to consider both the type of infection prevented, that is, whether major or minor wound infection or UTI and the overall usage of antibiotics in the groups under comparison. Clinical and surgical variables characteristic of the centre may be of importance in determining the success of a particular regimen. Comparative studies of the efficacy of different antibiotics for chemoprophylaxis should be carried out at the same centre and by the same investigators. For vaginal hysterectomy, such studies are reported by Grossman *et al.* (1979) and Hamod *et al.* (1980) who compared cefazolin with penicillin, and cephalothin with metronidazole respectively. No significant difference was found between the regimens under comparison, but the number of patients involved was small. For abdominal hystrectomy, Grossman *et al.* (1979) compared cefazolin and penicillin, Houang *et al.* (1984) compared ampicillin plus sulbactam with metronidazole, and Hemsell *et al.* (1984) compared cefoperazone and cefoxitin. No significant differences were found in these studies; the spectra of antimicrobial activities of the antibiotic regimens under comparison were quite similar. Contrarily, Giles *et al.* (1984) reported a significant reduction in both the infection at operative sites and in UTI (5% vs 15%; and 1% vs 31% respectively) when cephradine (three doses) plus metronidazole (seven doses) were used when compared with metronidazole alone (seven doses). Furthermore, 43 additional courses of antibiotics were required in those receiving metronidazole alone compared with 14 courses in those treated with cephradine plus metronidazole. The combination of cephradine and metronidazole is active against the aerobic as well as the anaerobic flora of the vagina. Additional studies are required to search for a safe and cost-effective regimen. By using antibiotics with different ranges of activity these studies may also define the pathogenesis of post operative infections following hysterectomy.

THERAPEUTIC ABORTION

Pelvic inflammatory disease is an important complication of therapeutic abortion. It occurs in 1.5% of all cases. Apart from the immediate post-operative morbidity, it may lead to permanent impairment of fertility (Westrom, 1975). Recently, workers have addressed themselves to the question of preventing infection after therapeutic abortion. The most common problems encountered by these investigations were (1) collection of data, and (2) diagnosis of pelvic infection. It is difficult to ensure a high follow-up rate either by questionnaire return or even by outpatient appointment. There are problems in the accurate diagnosis of pelvic infection, particularly using questionnaires. Furthermore, different surgical procedures, e.g. post-conception prostaglandin, vacuum aspiration, or intrauterine prostaglandin, may be employed at different centres for different stages of pregnancy. These factors make it difficult to compare the infection rates between studies.

Chemoprophylaxis may be given routinely to all patients undergoing therapeutic abortion. The results of three such studies are tabulated in table 3. All

TABLE 3. — *Placebo-controlled prophylactic trials for therapeutic abortion.*

Study	Antibiotics and regimen	Total number of patients	% of patients with infection	
			Placebo	Rx
1975 Hodgson	Tetracycline (4 days)	4,000	9	3
1980 Brewer	Doxycycline (1 dose)	2,950	0.6	0.07 *
1981 Sonne-Holm	Penicillin+Pivampicillin (4 days)	493	10.9	5.5 *

* $p <$ Placebo vs treatment

were placebo-controlled, but only the study by Sonne-Holm *et al.* (1981) was randomized. Significant reductions in pelvic infection were reported in the two more recent studies (Brewer, 1980, Sonne-Holm *et al.*, 1981). However, the wisdom of chemoprophylaxis was questioned by MacKenzie and Fry (1981) who found the incidence of suspected post-abortion infection and secondary subfertility in therapeutic abortion similar to that following spontaneous abortion and full-term delivery. The use of prophylactic antibiotics for every patient is not therefore justified.

Furthermore, the regimens used for prophylaxis may be inadequate for treatment of existing infections. Qvigstad *et al.* (1983) found no protective effect against the development of pelvic inflammatory disease (PID) in women who had positive cervical culture for *Chlamydia trachomatis* when a single dose of tetracycline (200 mg i.v.) was given at the time of therapeutic abortion.

An alternative approach it to define the risk factors associated with the development of post-operative PID, and only administer prophylaxis where it is appropriate. Sonne-Holm *et al.* (1981) reported that prophylaxis caused a significant reduction in post-operative PID only in those women who had previously suffered from this condition. The rate of infection in this group was 22.4 per cent among those receiving placebo and 2.1% among those receiving antibiotics. For women without previous history of PID, the infection rate was similar between the antibiotic and placebo group. They therefore suggested that only women who had earlier had PID should be given chemoprophylaxis.

Other risk factors associated with post-operative PID include the presence of genital tract infections. Endometriosis after therapeutic abortion is three times more common in women with untreated gonorrhoea (Burkman *et al.*, 1976). Other organisms including *Chlamydia trachomatis* and *Mycoplasma hominis* have been found in association with acute PID (Mardh, 1980). The presence of chlamydia in the cervix at the time of therapeutic abortion appears to be associated with a high incidence of post-operative PID. Qvigstad *et al.* (1982) reported that chlamydia were isolated from the cervix of 30/213 (13.8%) women before termination of pregnancy. During the first 2 post-operative weeks, 7/30 (23.3%) developed PID. In a subsequent report, they also noted that younger women are more likely

TABLE 4. — *Results of microbiological screening for cervical carriage of N. gonorrheae and C. trachomatis.*

	No. of pt.	% (+) Culture	
		Gonococcus	Chlamydia
1979 Singha and Balsdon	160	2	Not done
1983 Ridgway *et al.*	89	0.01	8
1984 Qvigstad	8	0.7	12.6
1984 Mills	500	2	2
1984 Houang (unpublished)	160	0.6	7

to develop PID. Of the chlamydia positive patients, 40% aged <20 years developed PID after abortion compared with 15% aged 20-30 years (Qvigstad *et al.*, 1983). Thus, the detection of specific genital tract infections pre-operatively with appropriate treatment of the infected women appears to be a rational alternative approach.

The incidence of cervical carriage of gonococci and chlamydia, the 2 important aetiological agents involved in PID, among women undergoing therapeutic abortion have been studied by several groups (table 4). The results vary from centre to centre. This may be due to the differences in the populations examined. The carriage rate of *C. trachomatis* is generally much higher than that for *N. gonorrhoeae*. There are several benefits from routine microbiological screening. Appropriate antibiotic treatment may be instituted before or soon after the surgical procedure, and will be valuable both in terms of immediate morbidity and as protection against development of PID at a later date. It also allows contact tracing thus preventing further spread of these organisms in the community. The laboratory procedures, however, are expensive, and the positivity rate is relatively low (10% in UK). Attention to detail is required to ensure optimum isolation rates. Bedside inoculation of culture medium, and immediate incubation in appropriate atmosphere is required for the isolation of *N. gonorrhoeae*, special transport medium and appropriate storage will facilitate the isolation of *C. trachomatis*.

In summary, there is inadequate evidence to support the use of chemoprophylaxis routinely for termination of pregnancy. Microbiological screening and subsequent appropriate treatment of genital tract infection is a rational approach to reduce the incidence of PID after therapeutic abortion. In centres where such facilities are not available, selective chemoprophylaxis based on a previous history of PID or age of the women may be employed. However, a suitable antibiotic prophylactic regime is yet to be proposed. Further work is required to define other risk factors associated with the development of post abortion PID.

REFERENCES

Bartlett J. G., Onderdonk A. A., Drude E., Goldstein C., Andkerka M., Abpert S., McCormack W. M.: *The Journal of Infectious Diseases, 136,* 271, 1977. – Berger S. A., Nagar H., Gordon M.: *The Journal of Reproductive Medicine, 24,* 185, 1980. – Breenden J. T., Mayo J. E.: *Obstetrics and Gynaecology, 43,* 379, 1974. – Brewer C.: *British Medical Journal, 281,* 780, 1980. – Burkman R. T., Tonasia J. A., Atienza M. F., King T. M.: *American Journal of Obstetrics and Gynecology, 126,* 648, 1976. – Duff P., Park R. C.: *Obstetrics and Gynecology, 55,* 193, 1980. – Garibaldi R. A., Burke J. P., Dickman M. L., Smith C. B.: *New England Journal of Medicine, 291,* 215, 1974. – Gifford R. H., Feinstein A. R.: *New England Journal of Medicine, 280,* 351, 1969. – Giles J. A., Asher R. G., Heap J. N. D., Hey F. M., Moloney M. D., Newman M. J., Pomeroy L., Scane J. M., Smith J. H., Wathen O. G., Hawkins D. F.: *Journal of Obstetrics and Gynaecology,* in press. – Grossman J. H., Greco T. P., Minkin M. J., Adams R. L., Hierholzer W. J., Andriole V. T.: *Obstetrics and Gynecology, 53,* 537, 1979. – Hamod K. A., Spence R., King T. M.: *Obstetrical and Gynecological Survey, 37,* 207, 1982. – Hamod K. A., Spence M. R., Rosenhein N. B., Dillon M. B.: *American Journal of Obstetrics and Gynecology, 136,* 976, 1980. – Hemsell D. L., Cunningham F. G., Kappus S., Nobles B.: *Obstetrics and Gynecology, 56,* 629, 1980. – Hemsell D. L., Johnson E. R., Bawdon R. E., Hemsell P. G., Heard M. L., Nobles B. J.: *Obstetrics and Gynecology, 63,* 467, 1984. – Hirschmann J. V., Inui T. S.: *Reviews of infectious diseases, 2,* 1, 1980. – Holman J. F., McGowan J. E., Thompson J. D.: *Southern Medical Journal, 71,* 417, 1978. – Houang E. T., Watson C., Howell R., Chapman M.: *Journal of Antimicrobial Chemotherapy,* in press. – Jandial L., Reid T. M. S., Jandial V.: *Research and Clinical Forums, 5,* 45, 1983. – Mărdh P. A.: *American Journal of Obstetrics and Gynecology, 138,* 933, 1980. – MacKenzie A., Fry A.: *British Medical Journal, 282,* 476, 1981. – Matthews D. D., Agarwal V., Gordon A. M., Cooper J.: *British Journal of Obstetrics and Gynaecology, 86,* 737, 1979. – Matthews D. D., Ross H.: *British Journal of Obstetrics and Gynaecology, 84,* 894, 1977. – Mendelson J., Portnoy J., de St. Victor J. R., Gelfland M. M.: *Obstretrics and Gynecology, 53,* 31, 1979. – Mickal A., Curole D., Lewis C.: *Obstetrics and Gynaecology, 56,* 222, 1980. – Mills A. M.: *British Journal of Obstetrics and Gynaecology, 9,* 182, 1984. – Øvigstad E., Skaug K., Jerve F., Fylling P., Ulstrup J. C.: *British Journal of Venereal Diseases, 59,* 189, 1983. – Øvigstad E., Skaug K., Jerve F., Vik I. S. S., Ulstrup J. C.: *British Journal of Venereal Diseases, 58,* 182, 1982. – Polk B. F.: *Journal of Antimicrobial Chemotherapy, 8,* 115, 1981. – Polk B. F., Tager I. B., Shapiro M., Goren-White B., Goldstein P., Schoebaum S. C.: *Lancet, 1,* 437, 1980. – Ridgway G. L., Mumtaz G., Stephens R. A., Oriel D.: *British Medical Journal, 286,* 1478, 1983. – Roberts J. M., Homesly H. D.: *Obstetrics and Gynaecology, 52,* 83, 1978. – Shepers J. J. P., Merkus F. W. G. M.: *Clinical Pharmacology and Therapeutics, 29,* 281, 1981. – Shapiro M., Munoz A., Tager I. B., Schebaum S. C., Pol B. F.: *New England Journal of Medicine, 307,* 1661, 1982. – Singha H. S. K., Balsdom M. J.: *British Journal of Clinical Practice, 33,* 163, 1979. – Sonne-Holm S., Heisterberg L. Hebjørn S., Dyring-Andersen K., Andersen J. T., Hejl B. L.: *American Journal of Obstetrics and Gynecology, 139,* 693, 1981. – Stage A. H., Glover D. D., Vaughan J. E.: *Journal of Reproductive Medicine, 27,* 113, 1982. – Thadepalli H., Gorbach S. L., Keith L.: *American Journal Obstetrics and Gynecology, 117,* 1034, 1973. – Walker E. M., Gordon A. J., Warren R. E., Hare M. J.: *British Journal of Obstetrics and Gynaecology, 89,* 957, 1982. – Westrom L.: *American Journal of Obstetrics and Gynecology, 121,* 707, 1975.