Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation. Observational longitudinal cohort study.

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Abstract

Objective: To determine the role, timing and indications for endometrial hysteroscopic investigation in relation to the clinical, ultrasound and histological features of the endometrium during tamoxifen use.

Methods: We performed an observational longitudinal cohort study (years 2007-2012) that investigated the endometria of 151 tamoxifen users with hysteroscopy and histology. For all patients, gynaecological history, years of adjuvant treatment, ultrasound endometrial thickness measurement and indications for hysteroscopy were recorded.

Results: Hysteroscopic findings showed that 100% of patients referred for simple follow-up had no evidence of endometrial disease. We found a strong correlation between previous history of abnormal uterine bleeding (with or without endometrial thickening) and hysteroscopic suspicion of endometrial atypia that was confirmed by histology. Hysteroscopy had 83.3% sensitivity, 99% specificity, 83.3% PPV and 99% NPV in detecting endometrial atypia. No significant correlation was found between endometrial thickening to >5 mm without bleeding and histological atypia. Similarly, the duration of treatment was not related to endometrial thickening and histological atypia.

Endometrial stromal hyperplasia was detected by histology in 70.5% of patients with endometrial thickness measurements ranging from 5-10 mm. In contrast, no atypia was detected when endometrial thickness was <5 mm.

Ultrasound performed using a 5-mm cut-off threshold for endometrial thickness resulted in 100% sensitivity, 15% specificity, 4% PPV and 100% NPV in detecting endometrial atypia, while a 10-mm cut-off threshold resulted in 84% sensitivity, 69% specificity, 10% PPV and 99% NPV.

Conclusion: Low-risk tamoxifen users do not require different endometrial surveillance than the general population. Hysteroscopy could play a fundamental role in determining the endometrial status of patients before the initiation of tamoxifen treatment and in assessing the endometrial status of patients when bleeding occurs.
Keywords

Endometrial surveillance, tamoxifen, breast cancer, adjuvant therapy, follow-up, hysteroscopy.
**Introduction**

Breast cancer is the most common cancer worldwide and the second most common cause of cancer death in the female population. [Siegel R et al. 2011] The breast cancer mortality rate has decreased in recent decades in developed countries as a result of increased screening and advances in adjuvant treatment. [Berry DA et al. 2005]

Randomized clinical trials demonstrated survival benefits associated with the use of adjuvant therapies, with estimated reductions in the annual odds of death ranging from 8 to 28%, depending on the type and duration of therapy, the age of the patient, and the characteristics of the tumour. [Aebi S et al. 2011]

Tumours with detectable (≥1%) expression of oestrogen receptors (ER) and/or progesterone receptors (PgR) are considered hormone-receptor positive and are usually well-differentiated with a low mitotic index and consequently, a good prognosis. [Hammond ME et al. 2010] In 75% to 80% of patients with early breast cancer who have ER-positive tumours, treatment with 5 years of tamoxifen (TAM) immediately and substantially reduces local, contralateral, and distant recurrence rates and decreases the 15-year breast cancer mortality rate. Therefore, tumours with high or uncertain hormone responsiveness (ER>1%) should be treated with endocrine therapy. [Dowsett M et al. 2010]

The Cochrane review performed by Clarke [Clarke MJ 2008] affirmed that years of adjuvant TAM treatment substantially improves the 10-year survival rate of women with ER-positive tumours or tumours of unknown ER status by reducing breast cancer recurrence and mortality.

However, it is universally accepted that standard TAM dosages may be responsible for endometrial proliferation, hyperplasia, polyp formation, invasive carcinoma, and uterine sarcoma. [ACOG 2006]

Recent data from Iqbal et al. [Iqbal J et al. 2012] showed that the risk ratio (RR) for endometrial cancer is low (RR: 1.19) in women receiving TAM therapy who are less than 50 years old but is significantly increased in those older than 50 years old (RR: 3.32).
Therefore, for many years patients treated with TAM strictly underwent yearly/half-yearly transvaginal ultrasound (TVS) examinations, often with subsequent hysteroscopic and histopathologic investigation.

Although there are not clearly-defined and universally accepted guidelines for follow-up examination of TAM-treated patients, the most common test used is endometrial surveillance. This approach can result in clinical overtreatment in women with no known risk of endometrial cancer who require only routine gynaecological care. It can also result in undertreatment in high-risk women.

Althuis et al. reported 13 years ago that half of breast carcinoma survivors were tested for uterine abnormalities and that 38% of TAM users never had a test despite their increased risk for abnormalities. The authors concluded that clear guidelines need to be established for early detection of uterine abnormalities among TAM-treated breast carcinoma patients to identify the most appropriate method and frequency of investigation. [Althuis MD et al. 2000]

Although ultrasound is the primary diagnostic tool for endometrial follow-up of postmenopausal patients, the absence of a defined endometrial thickness cut-off for the TAM-treated subgroup reduces ultrasound accuracy and increases the number of patients referred for unnecessary hysteroscopy. [Dijkhuizen FP et al. 1996, Bertelli G et al. 1998]

Despite the high accuracy of hysteroscopic investigation, significant TAM-related endometrial changes occur throughout the years of treatment, including atrophic-cystic, hypervascularization, endometrial polyps, and lesions suspicious for malignancy. Poor understanding of the severity of these potential side effects of TAM treatment could be responsible for the use of invasive and costly diagnostic procedures (e.g., endometrial biopsy) that often give negative results, particularly in absence of reports of abnormal uterine bleeding (AUB). [Pérez-Medina T et al. 2011]

The aim of this study is to determine the role, timing and indications for endometrial hysteroscopic investigation in TAM-treated patients in relation to the clinical, sonographic and histological features of the endometrium.
Material and Methods

We performed an observational longitudinal cohort study on patients referred to the hysteroscopic service of the endoscopy unit of the gynaecologic and obstetric clinic at Padua University from June 2007 – June 2012.

All enrolled patients were properly informed about the aim of the study, and they consented in a written consent form describing the use of their privacy data (Italian law 675/96).

All patients were consecutively enrolled by the researcher who conducted the hysteroscopic examination.

Eligible patients were recruited from a large cohort of patients with previous surgically treated breast cancer. All patients were positive for ER and were taking TAM as adjuvant treatment after adequate chemotherapy or radiotherapy according to international guidelines. [ABSG 2009, Aebi S et al. 2011, NCCN 2011] Patients received annual gynaecological exams in combination with TVS and pelvic sonography.

All patients received an office hysteroscopy with a continuous-flow hysteroscope (Karl Storz®) using saline solution as a distension medium and 30° angle view optics (2.9 mm diameter).

The indications for a hysteroscopy referral were asymptomatic endometrial thickening to more than 5 mm (Group A_ind), AUB without sonographic evidence of endometrial thickening (Group B_ind), AUB with sonographic evidence of endometrial thickening (Group C_ind) or endometrial monitoring in cases with no previous signs of AUB or endometrial thickening (Group D_ind).

We collected the following data about each patient: age, parity, hormonal status (premenopausal, perimenopausal, and physiologic or iatrogenic postmenopausal), previous Oestrogen Progesterone Therapy (EPT), duration of TAM treatment (Group A_tam: 1 year; Group B tam: 2 years; Group C_tam: 3 or more years), and endometrial thickness measured within 30 days before hysteroscopic investigation (Group A_eco: <5 mm; Group B_eco: between 5 and 10 mm; Group C_eco: >10 mm).
We also reported the following hysteroscopic findings: endometrial atrophy (Group A\textsubscript{hys}); endometrial atrophy with areas of focal hyperplasia (Group B\textsubscript{hys}); endometrial polyps without atypia (Group C\textsubscript{hys}); endometrial hyperplasia with suspicion of atypia or unusual polyps (Group D\textsubscript{hys}); and suspected endometrial cancer (Group E\textsubscript{hys}).

For all patients, an office endometrial biopsy or resectoscopy (i.e., polyp removal or focal endometrial resection) was performed, which enabled histological diagnosis and appropriate therapy.

Histological findings were grouped into the following categories: negative for neoplasia (Group A\textsubscript{istol}); glandular hyperplasia without atypia (Group B\textsubscript{istol}); stromal hyperplasia with or without oedema or fibrosis (Group C\textsubscript{istol}); glandular hyperplasia with atypia (Group D\textsubscript{istol}); and endometrial cancer (Group E\textsubscript{istol}).

We excluded patients from the study with inadequate samples for histological diagnosis, absent previous TVS, discontinuous TAM treatment, concomitant or previous adjuvant aromatase inhibitor therapy, previous LH-RH analogues and absent or ambiguous histology.

Our primary goal was to compare histological diagnosis with indications for hysteroscopic investigation.

Our secondary goal was to analyse the correlation between the duration of treatment, endometrial thickness and histology and the correlation between endometrial thickness and detection of stromal hyperplasia.

We also compared the detection rate of endometrial atypia and endometrial thickness. Finally we report the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TVS (cut-off of 5 or 10 mm) and hysteroscopy for detection of atypical or malignant endometrial lesions.

Statistical analysis was performed using SPSS statistical software (Chicago, IL) version 19 for Windows. The results were expressed in absolute numbers and percentages for discrete variables and in average ± standard deviation for continuous variables.
We performed appropriate parametric and nonparametric statistical tests when possible using the Kolmogorov-Smirnov test as a normal distribution of the sample. Continuous variables were analysed by t-test, and categorical variables were analysed by the $\chi^2$ test or Fisher's exact test. P-values of $p<0.05$ were considered statistically significant.
Results

For this study, we recruited 455 patients with a history of breast cancer and subsequent TAM therapy. Among them, only 151 patients, ranging in age from 35 – 85 years old (mean age 58.31 ± 10.86 years), were eligible for the study. (Table 1)

Data describing parity, hormonal status, menopause duration, years of TAM treatment, endometrial thickness, hysteroscopic indications and findings, and histological diagnosis are reported in Table 1. Analysis of the relationship between the indications for office hysteroscopy and hysteroscopic findings showed that 100% of patients referred for simple follow-up had no hysteroscopic evidence of disease. (p<0.01)

We also found a strong correlation between previous history of AUB (with or without endometrial thickening) and hysteroscopic evidence of atypia, which was independent from the indications for hysteroscopy. (p<0.01)

In no case of endometrial thickening without signs of AUB did the hysteroscopic features suggest a suspicion of atypia.

In our sample, a comparison of hysteroscopic reports and histological diagnosis showed that hysteroscopy had 83.3% sensitivity, 99% specificity, 83.3% PPV and 99% NPV in detecting atypia. (Table 2)

All cases of endometrial biopsy in patients receiving hysteroscopic investigation with the intent of follow-up and in the absence of clinical symptoms were negative for atypia. (p<0.001)

However, 83.3% of the histological endometrial atypia cases were detected in patients with a previous history of AUB, and only in 1 case (16.7%) was the patient asymptomatic and referred to hysteroscopy on the basis of endometrial thickening. (p<0.05)

With the exception of this single case, no significant correlation was found between endometrial thickening (> 5 mm) without AUB and histological atypia.

We did not find any statistically significant correlation between the duration of treatment and endometrial thickening. However, over 50% of the TAM-treated patients had endometrial thickness
between 5 and 10 mm. In particular, the thickening was detected in 53.5% of patients during the first year of treatment, in 51.2% during the second year and in 53.7% after the second year. There was no significant correlation between TAM treatment duration and the histological diagnosis of atypia. However, it is important to note the following trend linking atypia to the duration of treatment: 1 case of endometrial atypia in the first year of therapy, 1 case of endometrial atypia in the second year of therapy and 4 cases of endometrial atypia after the second year of therapy. The overall rate of atypia detection was 2.3% in the first year, 2.4% in the second year and 6% after the second year of treatment.

Stromal hyperplasia with or without oedema and fibrosis was detected histologically in 70.5% of patients with endometrial thickness between 5 and 10 mm. In contrast, no stromal hyperplasia was detected in patients with endometrial thickness less than 5 mm. (p<0.01)

Interestingly, we observed that of the patients with endometrial thickness less than 10 mm (102 patients), only 1 had endometrial atypia (0.98%), which occurred along with AUB. All remaining cases of endometrial atypia were detected in patients with endometrial thickness greater than 10 mm. (p<0.01)

Finally, TVS detected endometrial atypia with 100% sensitivity, 15% specificity, 4% PPV and 100% NPV when an endometrial thickness cut-off value of 5 mm was used. TVS detected endometrial atypia with 84% sensitivity, 69% specificity, 10% PPV and 99% NPV when a cut-off value of 10 mm was used. (Table 2)
Discussion

TAM, like all selective oestrogen-receptor modulators (SERMs), acts as an oestrogen agonist or antagonist in different tissues. This feature is related to the specific actions of TAM on at least two distinct ERs whose proportions differ depending on the tissue type. [Aebi S et al. 2011]

TAM has been approved by the United States Food and Drug Administration with the following indications: adjuvant therapy of breast cancer, metastatic breast cancer and reduction of the incidence of breast cancer in high-risk women. [Siegel R et al. 2011]

Endometrial polyps are the most commonly diagnosed pathologies in TAM-treated patients, especially in postmenopausal women. [Osborne CK 1998, Deligdisch L et al. 2000, Polin SA et al. 2008]

Similarly, 25.2% of hysteroscopic examinations in our sample revealed the presence of one or more endometrial polyps (58.2% of non-negative reports). Moreover, only in one case was endometrial glandular atypia reported (2.6%), which is similar to the findings of Cohen et al. and Ramondetta et al. [Ramondetta LM et al. 1999, Cohen I 2004]

Most of the uncertainty regarding TAM use is related to the increased risk of endometrial atypia and subsequent cancer development, while only in rare cases has TAM been reported as a risk factor for mixed Müllerian tumours. [Wickerham DL et al. 2002, Curtis RE et al. 2004] A meta-analysis conducted by Braithwaite et al. based on 32 clinical trials and including 52,929 patients has shown that the risk of endometrial cancer is significantly increased in women taking TAM to an estimated relative risk of 2.7. [Braithwaite RS et al. 2003]

Even if the use of TAM increases the risk of preneoplastic and neoplastic endometrial disease, several large-scale randomized clinical trials have shown that the therapeutic benefit of TAM for adjuvant treatment of breast cancer exceeds the risks related to stimulation of the endometrium. [Cuzick J et al. 2002, Fisher B et al. 2005, Bevers TB et al. 2010, EBCTCG 2011]

Despite the widespread use of TAM, there currently are no universally accepted international guidelines for its use, with the exception of the 2006 ACOG committee opinion. This may be
because the studies on TAM treatment have reported data from heterogeneous populations with recurrent bias related to unknown endometrial status prior to treatment. [ACOG 2006]

Nevertheless, ACOG recognized the importance of hormonal status in estimating the risk linked to TAM-treatment, because premenopausal women have no known increased risk for endometrial cancer and require no further investigation beyond routine gynaecological checks.

In fact, our data indicate that of 31 premenopausal patients, only 2 (6%) developed endometrial atypia and none developed endometrial cancer. This is comparable to the incidence of endometrial hyperplasia with atypia in the general population reported by Cohen et al. and Polin et al. [Cohen I 2004, Polin SA et al. 2008]

For postmenopausal women, ACOG recommended an annual gynaecological check-up in the absence of symptoms related to the development of endometrial hyperplasia (e.g., AUB, spotting and vaginal discharge). However, they did not define the most appropriate algorithm for following women at increased risk for endometrial disease.

According to ACOG suggestions, AUB is the clinical sign most commonly linked to endometrial disease that requires investigation to exclude the possible onset of endometrial atypia. [Love CD et al. 1999, Seoud M et al. 1999] In fact, our data showed that the 83,3% of histological endometrial atypia was preceded by AUB.

Currently there is abundant scientific evidence [Garuti G et al. 1999, Bronz L 2000, Litta P et al. 2005, Guruwadayarhalli B et al. 2007, Tinelli R et al. 2008] that hysteroscopic examination is the gold standard for the management of AUB, with curettage of the uterine cavity required only for treatment of haemostatic urgencies and when active bleeding is present.

A study of 310 TAM-treated patients by Giordano et al. found that hysteroscopy has 96% PPV and 65% NPV for atypical endometrial hyperplasia or endometrial cancer. [Giorda G et al. 2002] Similar to our results, Ceci et al. [Ceci O et al. 2003] reported 97% sensitivity, 100% specificity, 100% PPV and 96% NPV of hysteroscopy relative to histological diagnosis.
On this basis, office hysteroscopy could be considered a safe, well-tolerated diagnostic test that enables targeted endometrial biopsies because it accurately distinguishes normal endometrium from pathologic endometrium and has a better sensitivity, specificity, PPV and NPV than ultrasound. [Garuti G et al. 1999, Garuti G et al. 2002, Taponco F et al. 2002, Tinelli R et al. 2008]

Although TVS is an effective test with a high NPV in postmenopausal women when endometrial thickness is less than 5 mm, its accuracy is reduced in TAM-treated patients. Currently, the debate over using TVS in TAM-treated patients is on-going, though numerous points have been clarified. In a study of 80 TAM-treated patients, Seoud et al. [Seoud M et al. 1999] showed that all patients who developed abnormalities had AUB but found no correlation between endometrial thickness and endometrial pathology. In this study, the only patient who developed endometrial cancer had endometrial thickness of 3 mm.

Recently, several authors [Dijkhuizen FP et al. 1996, Cheng WF et al. 1997, Bertelli G et al 1998, Polin SA et al. 2008, Goldstein SR 2010] attempted to improve the PPV of TVS in detecting endometrial atypia during TAM therapy. In a study of 164 asymptomatic women with previous breast cancer and TAM treatment, Bertelli et al. [Bertelli G et al 1998] reported no correlation between endometrial thickness greater or equal to 5 mm (54% of patients) and endometrial atypia. The authors concluded that in the absence of symptoms, it is not recommended to base routine follow-up on ultrasound and biopsy.

Fung et al. [Fung MF et al. 2003] reported that 32% of 304 TAM-treated patients had endometrial thickening. Of these, only six patients had endometrial atypia that was always associated with AUB. In an attempt to improve the PPV of ultrasound examination, these authors proposed a 9-mm cut-off that achieved 63.3% sensitivity with 43.3% PPV. They concluded that ultrasound is not recommended for the screening of endometrial abnomormalities in asymptomatic TAM-treated women.

Other large-scale studies have proposed cut-off values > 5 mm, resulting in approximately 50% false positives. [Dijkhuizen FP et al. 1996, Love CD et al. 1999] This percentage is not improved
with the help of the Doppler flowmetry, which results in 84, 1% sensitivity and 58.2% specificity for cut-off values up to 10 mm. [Fong K et al. 2003]

Our results agree with most recent evidence, showing that a cut-off of 5 mm for ultrasound has 100% sensitivity, 15% specificity, 4% PPV, and 100% NPV; these values are more acceptable than previous results but not satisfactory. However, by moving the cut-off to 10 mm we obtained 84% sensitivity, 69% specificity, 10% PPV and 99% NPV.

In 1995, Achiron et al. [Achiron R et al. 1995] explained the low accuracy of TVS in atypia detection by demonstrating that TAM-induced stromal hypertrophy is responsible for the apparent endometrial thickening observed by sonography. This concept was subsequently investigated by other authors [Achiron R et al. 1995, Neis KJ et al. 2000, Gao WL et al. 2011] who reported that TAM may have a pro-oestrogen effect in the cells of the endometrial stroma in postmenopausal women, inducing specific changes in the endometrium. These findings explain the discrepancy between the sonographic, hysteroscopic and histological reports. [Gao WL et al. 2011] Neis et al. [Neis KJ et al. 2000] performed hysteroscopic endometrial biopsies in 89 patients with sonographic endometrial thickening and found stromal hyperplasia associated with glandular atrophy and no atypia in 37% of cases.

The evidence that TAM has a pro-proliferative role in the stroma was confirmed by Decensi et al. [Decensi A et al. 1996] such that all patients with sonographic endometrial thickening had stromal proliferation directly proportional to the duration of treatment. We had similar results, with no evidence of benign stromal lesions in patients with endometrial thickness <5 mm in ultrasounds, while 70.5% of patients with a diagnosis of benign stromal lesions had endometrial thickness between 5 and 10 mm.

In postmenopausal TAM-treated women, the increased atypia risk, the low sensitivity of TVS for endometrial atypia detection and the high sensitivity of hysteroscopy lead many oncologists to suggest follow-up hysteroscopy even in the absence of AUB with or without TVS thickening. [Althuis MD et al. 2000, Taponeco F et al. 2002]
Although hysteroscopy has a high predictive value and specificity for the diagnosis of endometrial atypia, it cannot be used in place of histological examination, which remains the gold standard. Our results showed no evidence of atypia when hysteroscopy was performed as simple follow-up in the absence of AUB, with or without endometrial thickening. This suggests that in asymptomatic women, there is no rationale for TVS follow-up and hysteroscopy.

Despite reports that the duration of TAM treatment is directly proportional to atypia onset, [ACOG 2006, EBCTCG 2011] we observed a positive trend but no significant correlation between the duration of treatment and the occurrence of endometrial atypia. This result could be affected by the small size of our sample (151 patients); therefore, it would be worthwhile to validate our results with prospective large-scale studies.

Although our data were obtained from a non-screened single series of 151 research participants, the results suggest that in clinical practice when the estimated risks are low and bleeding is absent, TAM users do not require different endometrial surveillance than the general population. Hysteroscopy could play a fundamental role both in determining endometrial status before the initiation of treatment and in assessing endometrial status when bleeding occurs.
Conflict of Interest

All authors declare no conflict of interest.
Funding

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Acknowledgements

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References


Table legend

Table 1. General, gynaecological, hysteroscopic, sonographic and histological features of study patients.

- **Group A\_tam**: 1 year of treatment with tamoxifen; **Group B\_tam**: 2 years of treatment with tamoxifen; **Group C\_tam**: more than 2 years of treatment with tamoxifen.
- **Group A\_eco**: <5 mm endometrial thickness; **Group B\_eco**: endometrial thickness between 5-10 mm; **Group C\_eco**: endometrial thickness >10 mm.
- **Group A\_ind**: asymptomatic endometrial thickening to more than 5 mm; **Group B\_ind**: uterine bleeding without sonographic evidence of endometrial thickening; **Group C\_ind**: abnormal uterine bleeding in association with sonographic endometrial thickening; **Group D\_ind**: endometrial monitoring in cases with no previous signs of abnormal uterine bleeding or endometrial thickening.
- **Group A\_hys**: endometrial atrophy; **Group B\_hys**: endometrial atrophy with areas of focal hyperplasia; **Group C\_hys**: endometrial polyps without atypia; **Group D\_hys**: endometrial hyperplasia with suspicion of atypia or unusual polyps; **Group E\_hys**: suspected of endometrial cancer.
- **Group A\_istol**: negative for neoplasia; **Group B\_istol**: glandular hyperplasia without atypia; **Group C\_istol**: stromal hyperplasia with or without oedema or fibrosis; **Group D\_istol**: glandular hyperplasia with atypia; **Group E\_istol**: endometrial cancer.

Table 2. Comparison of transvaginal sonography (TVS) with 5 mm or 10 mm cut-off and hysteroscopy relative to atypia detection that is histologically confirmed.
Table 1. General, gynaecological, hysteroscopic, sonographic and histological features of study patients

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<th>Number</th>
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<td>41 (27.2)</td>
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<td>Group C_tam</td>
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<td>Endometrial thickness (mm)</td>
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<td>Group E_istol</td>
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**Table 2.** Comparison of transvaginal sonography (TVS) investigation with 5 mm or 10 mm cut-off and hysteroscopy relative to atypia detection that is histologically confirmed.

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<td>0.44-0.97</td>
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<td>NPV</td>
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</tbody>
</table>

95% CI was estimated by Wilson method and by binomial exact test, when necessary.