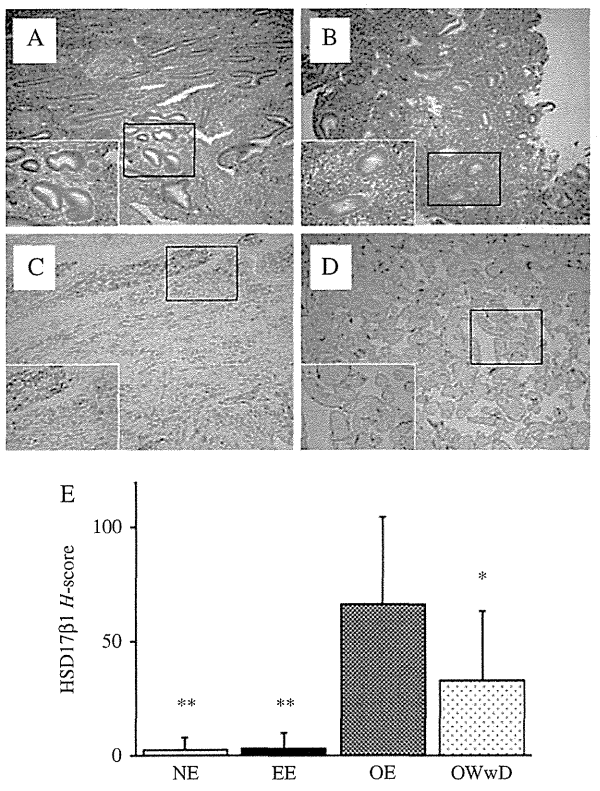

Figure 2
Representative immunohistochemical staining of 17β-hydroxysteroid dehydrogenase 1 (HSD17β1) in (A) normal endometrium (NE), (B) endometrium with endometriosis (EE), (C) ovarian endometrioma (OE), and (D) normal term placenta as a positive control. (E) The immunostaining intensity of NE ($n=19$), EE ($n=10$), OE ($n=23$), and OE treated with dienogest (OE w/D) ($n=11$) was scored with semi-quantitative index *H*-scores. Areas shown at a higher magnification are indicated by rectangles. Data are presented as means±S.E.M. *P* values are based on an unpaired *t*-test. *$P<0.05$ and **$P<0.01$ versus OE.

the expression of *HSD17β1* mRNA compared with the controls. However, DNG or P_4 did not significantly suppress *HSD17β2*, *HSD17β7*, *HSD17β12*, *STS*, or *EST* mRNA expression (Fig. 1B). In parallel with the mRNA results, DNG (10^{-7} M ($P<0.01$) and 10^{-6} M ($P<0.01$)) and P_4 (10^{-8} M ($P<0.05$), 10^{-7} M ($P<0.01$), and 10^{-6} M ($P<0.01$)) significantly suppressed the catalytic activity of HSD17β1 (Fig. 1C).

Immunohistochemistry

Immunohistochemical analysis showed HSD17β1 expression in the cytoplasm of epithelial cells and SCs of NE (Fig. 2A), EE (Fig. 2B), and OE (Fig. 2C). The immunostaining intensity of HSD17β1 was greater in OESCs when compared with NE ($P<0.01$) and EE ($P<0.01$). Moreover, there was a significant reduction in the immunostaining intensity in the OE w/D group ($P<0.05$) (Fig. 2E).

Discussion

In this study, we demonstrated DNG-mediated inhibition of mRNA expression, catalytic activity, and protein expression of HSD17β1 in endometriosis. Taken together with the previous findings that DNG inhibits aromatase in endometriosis (Shimizu *et al.* 2011, Yamanaka *et al.* 2012), DNG exerts comprehensive inhibition of abnormal estrogen production by the inhibition of two key enzymes that regulate estradiol production (Fig. 3). These actions of DNG contribute, in part, to its therapeutic effect on endometriosis.

In order to comprehensively examine the expression patterns of estrogen-metabolizing enzymes in OESCs compared with those in EESCs or NESCs, we employed a three-dimensional spheroid culture system characterized by multicellular aggregates of cells and extracellular matrices. This culture system produces sufficient baseline levels of proinflammatory factors (Enzerink *et al.* 2009, Vaheri *et al.* 2009), and spheroids of human immortalized endometrial epithelial cells (Shimizu *et al.* 2011) and primary cultured OESCs (Yamanaka *et al.* 2012) express higher levels of aromatase, COX2, and prostaglandin E_2 compared with the corresponding monolayer cultures. The results of this study indicated that HSD17β1 localizes in the cytoplasm of both epithelial cells and SCs. In OE, however, the majority of cells are SCs. Thus, the OESC

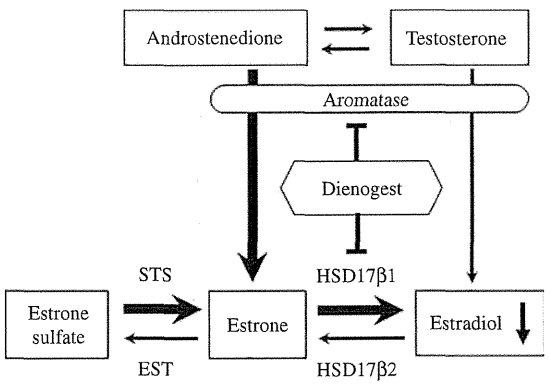

Figure 3
Scheme summarizing dienogest inhibition of estrogen production in endometriosis. Dienogest inhibits both aromatase and 17β-hydroxysteroid dehydrogenase 1 (HSD17β1), the key enzymes in estradiol biosynthesis. STS, steroid sulfatase; EST, estrogen sulfotransferase; HSD17β2, 17β-hydroxysteroid dehydrogenase 2.

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spheroids are considered to mimic the local environment of enzyme expression.

In the spheroid-cultured OESCs, we detected very low level of aromatase mRNA expression, whereas it was not detectable in EESCs or NESCs. This is in agreement with results from earlier studies, in which aromatase is only detectable in studies using immunohistochemistry and those using homogenized specimens just after sampling but not in monolayer cultured cells (Kitawaki *et al.* 1997, Dassen *et al.* 2007, Smuc *et al.* 2007). In OESCs, we detected overexpression of HSD17β1 mRNA and protein levels, responsible for activating estrogenic potency, whereas very low levels of mRNA and protein expression were observed in EESCs and NESCs. In contrast, the mRNA expression of HSD17β2, responsible for weakening estrogenic potency, was significantly lower in OESCs compared with EESCs and NESCs. This balance between the expressions of the two enzymes indicates that estradiol is more likely to be produced in OESCs compared with eutopic endometrium, which is concordant with results from previous studies (Zeitoun *et al.* 1998, Matsuzaki *et al.* 2006).

Furthermore, the expression of STS, also responsible for activating estrogenic potency, was significantly higher in OESCs compared with EESCs and NESCs, which is also consistent with previous findings (Utsunomiya *et al.* 2004, Colette *et al.* 2013). Dassen *et al.* (2007) reported high STS mRNA expression in both eutopic and ectopic endometrium, but no difference between the two tissues.

In contrast to the high levels of expression of STS, we detected very low levels of mRNA expression of *EST*, responsible for inactivating estrone in OESCs, whereas it was not detectable in EESCs or NESCs. Colette *et al.* (2013) reported very low levels of *EST* mRNA expression in both eutopic and ectopic endometrium, but found no difference between the two tissues. Utsunomiya *et al.* (2004) showed that *EST* was expressed in the endometrium but only during the secretory phase. In this study, we obtained specimens during the proliferative phase to eliminate the effect of P_4. This balance of the STS and EST expression indicates that estrone is more favorably produced in OESCs as well as EESCs and NESCs during the proliferative phase. The significance of the differences in expression of STS and EST between these cells remains to be elucidated.

Using this experimental model, it was determined that DNG significantly inhibited *HSD17β1* mRNA expression and its enzyme activity at 10^{-7} M in OESCs. These concentrations are equivalent to the blood level of mice administered 1 mg of DNG twice daily and patients administered 2 mg of DNG daily (Meriggiola *et al.* 2002, Sasagawa *et al.* 2008). The *in vitro* inhibitory effects of DNG are supported by the *in vivo* data from this study, demonstrating that DNG treatment for 3–5 months resulted in decreased HSD17β1 protein expression in OE.

The conversion of estrone to estradiol is also mediated though HSD17β7 and HSDβ12 as well as HSDβ1 (Moeller & Adamski 2006). DNG inhibited only *HSD17β1* but not *17HSDβ7* or 12 mRNA expression, which indicates that DNG reduces local estrogen production by the suppression of HSD17β1 in human OESCs.

We and other researchers have shown that the PR is involved in the mechanism of DNG-inhibited cell proliferation (Okada *et al.* 2001, Shimizu *et al.* 2009) and the expression of inflammatory factors (Mita *et al.* 2011), nerve growth factor, (Mita *et al.* 2014), and aromatase (Yamanaka *et al.* 2012). Although the *HSD17β1* gene lacks a P_4-responsive element in its promoter region, progestins including DNG downregulated *HSD17β1* and upregulated *HSD17β2* expression in immortalized endometriotic epithelial cells (Beranic & Rizner 2012). DNG inhibits the DNA-binding activity of NFκB, a key regulator of various pathological and inflammatory responses in endometriosis such as interleukin-8 production in human OESCs (Horie *et al.* 2005, Shimizu *et al.* 2011, Yamanaka *et al.* 2012). Bulun proposed a vicious cycle of an estrogen-dependent mechanism of endometriosis growth (Bulun 2009). Estradiol produced locally by aromatase stimulates tissue growth of endometriosis and upregulates COX2 via ERβ activation. COX2 overexpression results in an excess of prostaglandin E_2, which further stimulates aromatase expression via the orphan nuclear receptor steroidogenic factor 1. Furthermore, ERβ activation downregulates PR, which leads to reduced induction of HSD17β2 via retinoic acid (Zeitoun *et al.* 1998). The combination of upregulation of aromatase and downregulation of HSD17β2 contributes to the abnormally high levels of estradiol in endometriotic tissue. In addition to inhibition of aromatase, DNG inhibits HSD17β1, resulting in further reductions in local estradiol concentration. This interrupts the vicious cycle of endometriosis growth and also relieves endometriosis-associated pelvic pain by inhibiting prostaglandin E_2 production. The effect of inhibiting HSD17β1 on endometriosis has been demonstrated (Delvoux *et al.* 2014) and several HSD17β1 inhibitors have been developed and used in preclinical studies (Day *et al.* 2008, Poirier 2011). DNG is widely used in clinics to treat endometriosis with fewer side effects. We believe that the identification of the molecular mechanisms behind the therapeutic effect of DNG described here will lead to better understanding of the pathophysiology of endometriosis.

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Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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3 内分泌療法からHRTへの移行

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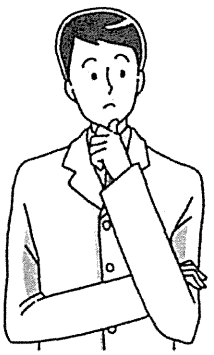

子宮内膜症治療において，内分泌療法からHRTへの切り替えの時期や適応について学ぼう！

1 はじめに

子宮内膜症は，子宮内膜またはその類似組織が子宮以外の部位で増殖，発育し，機能する疾患であり，性成熟期女性の約10%が罹患する良性の慢性疾患である。主として，腹膜病変，子宮内膜症性卵巣嚢胞，深部病変を形成する。症状は，月経痛や慢性骨盤痛などの疼痛，および不妊である。これらによって，思春期以降の発生から閉経に至るまで女性の各ライフステージにおいてquality of life（QOL）を著しく損ねる。

子宮内膜症の基本的な治療方針は，正確な臨床子宮内膜症の診断のもとに，まず不妊，子宮内膜症性卵巣嚢胞，疼痛の3項目の治療の要因を十分に分析する。その上で，無治療での経過観察，薬物療法，手術療法，そして生殖補助医療（assisted reproductive technology；ART）のなかから最も適切な治療方針を選択する。したがって，治療方針は患者の年代によって異なってくる。

本稿では，このうち40歳代から閉経後の女性における子宮内膜症の問題点とその対策について，特に子宮内膜症性卵巣嚢胞の取り扱い，疼痛の治療，そして内分泌療法から閉経後のホルモン補充療法（hormone replacement therapy；HRT）への移行について述べる。

2 挙児希望がない40歳代患者の子宮内膜症性卵巣嚢胞の取り扱い

挙児希望がない40歳代の場合には，子宮内膜症性卵巣嚢胞と疼痛のコントロールを中心に方針を考慮する。欧州生殖医学会（European Society of Human Reproduction and Embryology；ESHRE）のガイドライン2005[1]では子宮内膜症

性嚢胞が直径4 cm以上であれば腹腔鏡下卵巣腫瘍摘出術を推奨していた。その理由として，組織学的に確定診断を得るため，感染リスクを軽減するため，採卵を容易にするため，そして排卵誘発の反応性を改善するためとしていた。さらに，体外受精（*in vitro* fertilization；IVF）の成績を改善するためには3 cm以上を適応としていた。しかし，ESHREガイドライン2014[2]では，3 cmを超える子宮内膜症性卵巣嚢胞を有する不妊女性において，ART前の嚢胞摘出術が妊娠率を改善するというエビデンスはなく，子宮内膜症性疼痛または卵胞へのアクセスを改善するためにART前の嚢胞摘出術を検討する，という記述に移行している。

一方，日本産科婦人科学会の取扱い規約[3]では，子宮内膜症性嚢胞の大きさだけではなく，年齢や画像診断などの要素を加えた手術適応を提唱している。これは，大きさあるいは年齢が増すごとに悪性転化率が高くなることを勘案してのことである。すなわち，40歳代では4 cm以上で切除すべきであるが，10 cm未満なら画像診断で充実部分が認められなければ経過観察可能としている。20歳代，30歳代の場合，10 cm以上なら切除すべきであり，CA-125値や画像診断などで鑑別診断を行うとしている。これらを総合して，産婦人科診療ガイドライン：婦人科外来編2014[4]では，1）年齢，嚢胞の大きさ，挙児希望の有無を考慮して経過観察・薬物療法・手術療法のいずれかを選択するが，破裂・感染・悪性化予防のためには手術療法が優先される，2）手術療法にあたっては，根治性と卵巣機能温存の必要性を考慮して術式を決定する，3）年齢，嚢胞の大きさ，充実部分の有無により悪性化のリスクが高い症例では患側卵巣の摘出を選択する，と述べている。

近年は40歳代でも挙児希望あるいは妊孕性温存希望例が多くなっているので，嚢胞摘出術，薬物療法，経過観察をする場合が多い。嚢胞摘出術を行う場合には，残存卵巣の予備能低下を最小限に抑える配慮が必要である。

凝固またはレーザーによる嚢胞内焼灼術は卵巣予備能低下を軽減できる。しかし，両術式を比較したメタ解析では，嚢胞の再発率，再手術率，術後の月経痛，性交痛，非月経時骨盤痛，妊娠率いずれをとっても有意に嚢胞摘出術が嚢胞内焼灼術より優れている[5]。

40歳代以上の内膜症性嚢胞の最大の懸念点は悪性転化である。全体の頻度は0.7%と内外の報告ともに一致している。腫瘍径が大きいほど，患者の年齢が高いほど悪性転化のリスクが高くなる[6]。したがって，卵巣予備能温存よりは再発予防と悪性転化予防に重点を置くべきである。取扱い規約[3]に示すとおり，4 cm以上で切除を考慮すべきである。

ごく最近のnested患者対照研究では，片側卵巣摘出術を受けた群はホルモン療法のみを行った群よりも有意にその後の卵巣癌発生率が低く，すべての可視的内膜症病巣を除去した群では有意に卵巣癌発生率が低かったとしている[7]。しかし，悪性転化症例のなかには，4 cm未満の内膜症性嚢胞からの発生例や，嚢胞摘出術を施行した側からの発生例も報告されている[8]ので，卵巣を温存する場合には十分なインフォームド・コンセントと最長でも3カ月ごとの検診が必要である。

3 挙児希望がない40歳代患者の子宮内膜症性疼痛の治療

1 ホルモン製剤による維持療法

産婦人科診療ガイドライン：婦人科外来編2014[4]では，子宮内膜症性卵巣嚢胞を伴わない子宮内膜症の治療方針として，1）疼痛には，まず鎮痛剤（NSAIDs）による対症療法を行う，2）鎮痛剤の効果が不十分な場合や子宮内膜症自体への治療が必要な場合は，低用量エストロゲン・プロゲスチン配合薬，ジエノゲストを第1選択，GnRHアゴニスト（GnRHa），ダナゾールを第2選択として投与する，3）薬物療法が無効な場合，または不妊症を伴う場合には手術による子宮内膜症病巣の焼灼・摘除，癒着剥離を行う，と述べている。

子宮内膜症の病巣および疼痛に対しては内分泌療法が有効であるが，短期間の治療ではしばしば再発する。再燃を長期間抑制するためには内分泌療法を長期間継続する工夫が必要である（表1）[9]。

低用量経口避妊薬（oral contraceptive；OC）/低用量エストロゲン-プロゲスチン製剤（low-dose estrogen-progestin；LEP），ジエノゲスト，レボノルゲストレル放出型子宮内システム（LNG-IUS）は長期間使用できる。

一方，GnRHaは最も治療効果が高い反面，その低エストロゲン症状に由来する骨塩量低下を防ぐために6カ月以内に投与を中止する必要がある。そこで，エストロゲンを同時に投与しながらGnRHaを長期に投与するアドバック療法がある。GnRHa先行投与法は，GnRHaに引き続き低用量ダナゾール，OC/LEP，あるい

表1 子宮内膜症の長期維持管理のための内分泌療法

単剤
・低用量OC/LEP
・ジエノゲスト
・レボノルゲストレル放出型子宮内システム
併用
・GnRHa先行投与法 低用量ダナゾール漸減 中用量OC/低用量OC/LEP ジエノゲスト
・GnRHa＋アドバック療法
・アロマターゼ阻害剤 プロゲスチンとの併用 低用量OCとの併用 GnRHaとの併用

（文献9より）

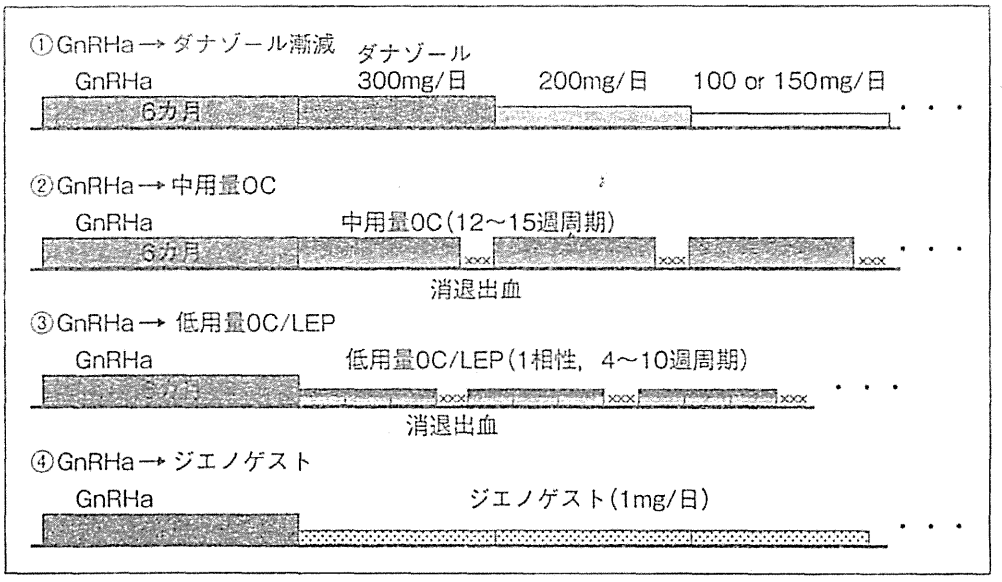

図1　GnRHaに引き続く維持療法
ダナゾール漸減，中用量エストロゲン・プロゲスチン，低用量OC/LEP，ジエノゲストのレジメン

はジエノゲストを長期間にわたって投与する方法であり，GnRHaによってもたらされた疼痛の抑制を維持する[10]。GnRHa先行投与後のジエノゲスト療法は，ジエノゲスト投与初期の不正子宮出血量を減少させる[11](図1)。

OC/LEPの最大の副作用である静脈血栓塞栓症（venous thromboembolism；VTE)のリスクは，非妊娠かつ非服用者で1～5/10,000婦人年であるのに対して，OC服用者では3～9/10,000婦人年と若干増加することが知られている。ただし，VTEリスクは年齢とともに上昇し，20歳代前半では1.32/10,000婦人年であるのに対して，40歳代前半では5.29/10,000婦人年と約4倍に増加する[12]ので注意が必要である。このことからも，50歳以上では使用すべきではない。これに対して，プロゲスチン単剤であるジエノゲスト，ジドロゲステロン，LNG-IUSは，40歳代においても年齢を要因とするリスク上昇はみられない。

2 深部子宮内膜症の腹腔鏡下切除術

子宮内膜症の病巣は，腹膜病変，子宮内膜症性卵巣嚢胞，そして深部子宮内膜症（deep infiltrating endometriosis；DIE）に大別される。

このうち，DIEは慢性骨盤痛，性交痛，排便痛，排尿痛などの深部疼痛をきたすことが多く，しかも内分泌療法に抵抗性であることが多い[13]。このことから，特に深部病巣を合併した重症の疼痛を訴える症例には腹腔鏡下手術を考慮する。手術にあたっては，安全でかつ過不足のない切除のために系統的な術式が整いつつある。一般に，後腹膜（pelvis side wall）を開窓，尿管を子宮動脈交差部まで剖出し，仙骨子宮靱帯から分離する。直腸側腔を同定し，直腸腟中隔側方を開放，そしてダグラス窩を開放する。さらに，膀胱子宮窩を開放する。このようにして

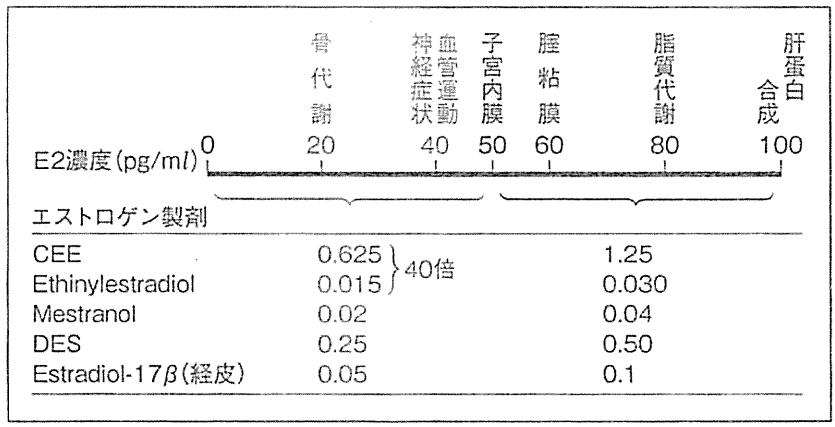

図 2　各組織での作用に必要な E2 濃度(therapeutic window)

(文献 15 より改変)

解剖を明らかにしつつ DIE を切除する。

4 HRT の方針

子宮内膜症に対する内分泌療法のリスクとベネフィットを踏まえた上で，40 歳代の適切な時期にこれを中止し，閉経後には HRT に移行する。閉経後 HRT による子宮内膜症の再燃は，多くの報告で 10%以下，ランダム化比較試験でも 3.5%であり[14]，影響は少ない。

閉経後の HRT として OC/LEP を使用し続けることが可能かという問題に関して，Barbieri[15]は，GnRHa 投与時の低エストロゲン症状を避けるために，血中エストラジオール（E2）濃度を子宮内膜症は縮小するが骨塩量は低下しない程度に保つ therapeutic window の理論を提唱している。この論文ではそれ以外に各種エストロゲン製剤の効力を比較している（図 2）。この図で HRT に通常使用される結合型エストロゲン（CEE）と OC/LEP に含まれているエチニルエストラジオール（EE）を比較すると，EE は CEE の 40 倍活性が強い。また，別の報告[16]では EE が CEE の 100 倍，E2 の 120 倍の活性を有している（表 2）。これを通常の服用量に当てはめて，HRT 時の CEE 0.625 mg と OC/LEP 中の EE 0.020～0.035 mg を比較すると，エストロゲン活性は OC/LEP が HRT より 1.3～6 倍強いことになる。したがって OC/LEP は，閉経後 HRT にはエストロゲン活性が強すぎである。

さらに，50 歳以上の女性において，ホルモン非使用者を対象とした VTE リスクは，OC 全体の補正オッズ比 6.3（95%信頼区間 4.6～9.8）に対して，経口 HRT は 1.7（1.1～2.5），非経口では 1.1（0.6～1.8）であった[17]。これらのことから，50 歳代あるいは閉経後には，OC/LEP の継続ではなく CEE または E2 に切り替えるべきである。

表2 各種エストロゲンの効力比較

	ホットフラッシュ	FSH抑制	HDLコレステロール	SHBG	CBG	アンジオテンシノーゲン
E2-17β	100	100	100	100	100	100
エストリオール	30	30	20			
エストロン-硫酸抱合		90	50	90	70	150
CEE	120	110	150	300	150	500
エクイリン-硫酸抱合			600	750	600	750
ジエチルスチルベストロール	100倍	340		2,560	2,450	1,950
エチニルエストラジオール	12,000	12,000	40,000	50,000	60,000	35,000

SHBG：sex hormone-binding globulin，CBG：corticosteroid-binding globulin （文献16より改変）

5 おわりに

40歳代において，子宮内膜症性卵巣嚢胞に関しては妊孕性温存から悪性転化予防に変遷していく時期であり，疼痛緩和に関しては長期間の抑制維持を目指すべきである。更年期には，内分泌療法からHRTへの円滑な移行が求められる。

KEY TAKE HOME

- 40歳代の子宮内膜症性卵巣嚢胞に対しては，4 cm以上で卵巣摘出術が推奨されている。挙児希望あるいは妊孕性温存希望例では，悪性転化の可能性に十分注意した管理が必要である。
- 40歳代の子宮内膜症性疼痛に関しては，長期にわたる内分泌維持療法を考慮する。薬物療法で制御できない深部病変による強い骨盤痛に対しては腹腔鏡下手術が必要となる。
- 閉経後のHRTには，OC/LEPのエストロゲン活性が強すぎることから，CEEまたはE2に切り替えるべきである。

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〔シンポジウム2／深部子宮内膜症の手術療法〕

根治性・機能温存・安全性を目指した深部子宮内膜症に対する腹腔鏡下手術

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緒　言

深部病変（deep infiltrating endometriosis；DIE）を有する子宮内膜症患者は月経痛，慢性骨盤痛，不妊を主症状とし，内分泌療法で十分な症状緩和が困難である場合には手術療法が必要となる．病変が骨盤臓器に浸潤して強度な癒着と骨盤臓器の解剖学的偏位を引き起こすため，手術を遂行するうえでは正確な癒着剝離と解剖学的再構築が必要となる．そのため，DIEを合併する子宮内膜症手術には根治性と機能温存とのバランスのみならず安全性の担保が重要となる．そこで，DIE症例の手術の有効性，手術完遂に有効な系統的癒着剝離と剝離デバイスの選択について検討した．

方　法

当科でのDIE症例に対する手術はすべて腹腔鏡下に行う．術式の選択に当たっては，年齢，症状，妊孕性温存希望の有無，病巣の進行度より総合的に判断し，根治性と機能温存のバランスを図る．子宮内膜症による骨盤内癒着を，①卵巣チョコレート嚢胞と後間膜後葉の癒着，②後腹膜腔（pelvic side wall）における尿管周囲の癒着，③直腸周囲の癒着（ダグラス窩閉鎖），④膀胱子宮窩の癒着に分類し，定型的にそれぞれの剝離すなわち系統的癒着剝離を行う（図1）．卵巣チョコレート嚢胞を有する場合その取扱いは，妊孕能温存を希望する場合は嚢胞切除もしくは焼灼を行い，卵巣実質をできるだけ温存して卵巣予備能低下の回避に努める．妊孕性温存を希望しない場合は，健側卵巣は温存して患側卵巣を切除する．子宮筋腫や子宮腺筋症を合併する場合は，子宮筋腫（腺筋症）核出術もしくは子宮全摘術の併用も考慮する．またrevised American Society for Reproductive Medi-

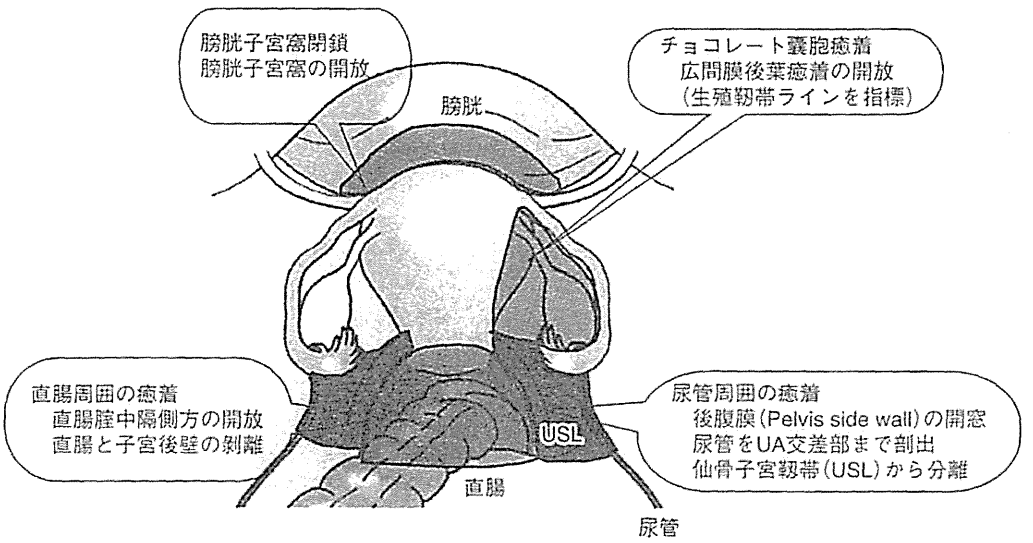

図1　子宮内膜症性骨盤内癒着の系統的剝離

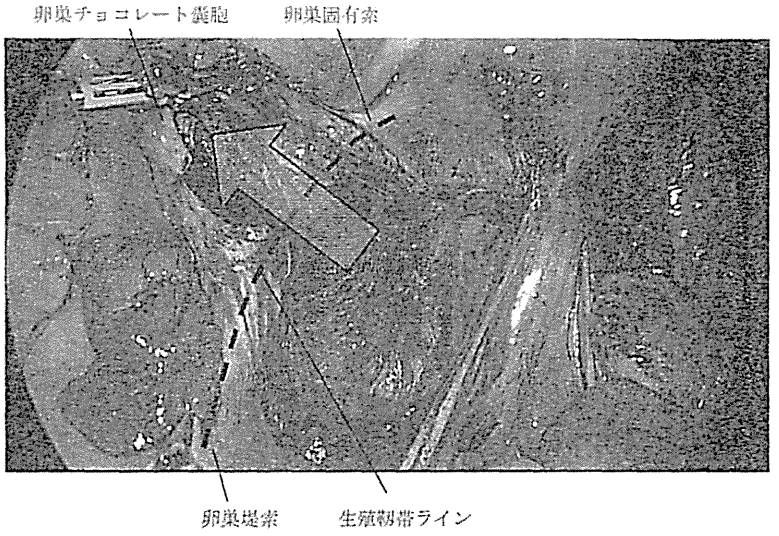

図2　生殖靱帯ラインを指標とした卵巣チョコレート嚢胞の剝離

図3　直腸腟間隙側方の展開

cine (r-ASRM) score〔1〕およびENZIAN score〔2〕によるDIEも含めた子宮内膜症病変の進行度の正確な評価を行うために，術前内分泌療法は原則として行っていない．

術式を示す．(1)臍部より5mmトロッカーを挿入してカメラ用ポートとし，気腹する．さらに，下腹部正中と左右側腹部に操作用ポートを留置する．(2)上腹部において横隔膜下腹膜病変の有無を確認する．(3)骨盤高位とし，骨盤内の病巣および癒着の評価を行う．(4)卵巣チョコレート嚢胞の後面を広間膜後葉や骨盤内臓器の癒着から外反させるように剝離する．剝離を行うにあたっては卵巣堤索と卵巣固有索を結ぶ生殖靱帯ラインを剝離限界の指標として必要十分に行い，血管損傷を回避する（図2）．続いてチョコレート嚢胞壁のstrippingもしくは付属器切除を行う．(5)広間膜後葉を開窓し，尿管を確認する．尿管がextrinsicタイプのDIEもしくは線維化により癒着もしくは狭窄している場合は，尿管を確認しながら子宮動脈交差部まで剝離を進め，広間膜後葉と仙骨子宮靱帯から遊離する．この過程で，岡林直腸側腔入口部を暫定的に展開する．続いて仙骨子宮靱帯内側より直腸腟中隔側方を展開する（図3）．(6)直腸の輪郭が明瞭になったところで直腸と子宮後頸部を鋭的に遊離する（図4）．(7)膀胱子宮窩にDIEを有する場合は，膀胱鏡を併用しながら膀胱子宮窩の剝離を行う．以上の過程で尿管周囲，直

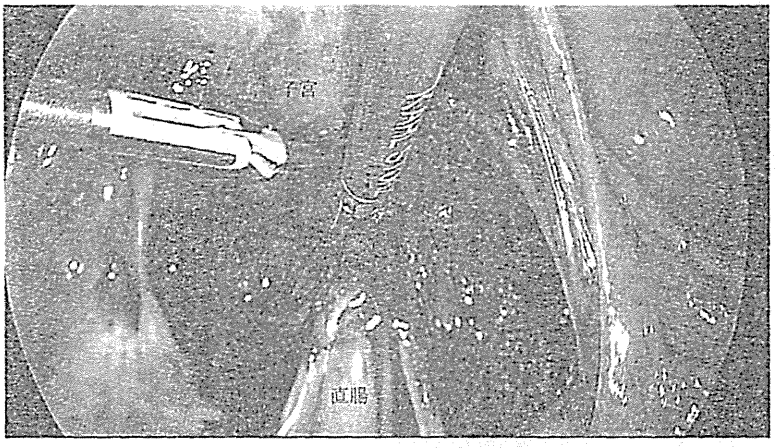

図4　直腸と子宮後頸部の遊離

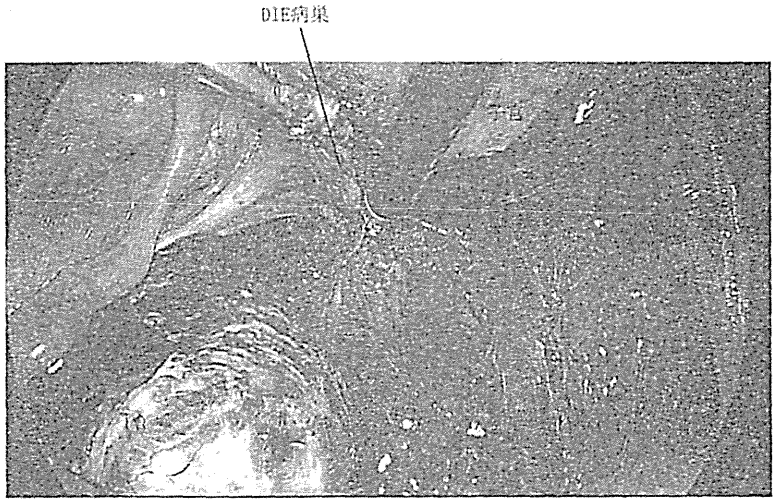

図5　直腸膣中隔のDIE病巣除去

腸側腔，直腸膣間隙周囲の系統的癒着剝離を行ったうえで，直腸膣中隔，仙骨子宮靱帯などに存在するDIE組織の病巣除去を行った(図5)．妊孕性温存を希望しない子宮筋腫あるいは子宮腺筋症を有する患者には，上記のごとく系統的癒着剝離を行った後に子宮全摘術を行い，引き続いてDIE病巣除去を行った〔3〕．

癒着剝離に使用するデバイスは，鈍的剝離には剝離鉗子，吸水管，当大学で共同開発されたロータリーヘッドダイセクター（図6）〔4〕，鋭的剝離には鋏鉗子，モノポーラ，超音波凝固切開装置を用いた．2009年4月から2014年12月までに当科で同一術者が施行した子宮内膜症腹腔鏡下手術症例230例のうちDIE合併例72例（表1）を後方視的に検討した．

結　果

骨盤内の子宮内膜症性癒着の剝離には，後腹膜腔を展開した系統的癒着剝離が有効で，安全かつ十分な骨盤内臓器の位置矯正，DIE病巣除去が可能であった．また状況に応じた剝離デバイスの選択も剝離の完遂に寄与した．対象症例のうち術前および術後1ヵ月の月経痛（VAS）を評価し得た44例を検討したところ，機能温存手術にDIE病巣除去術を併用した18例の術後1ヵ月後の月経痛の改善率は76.3%，DIE病巣除去術を併用しなかった15例の術後1ヵ月後の月経痛の改善率は60.2%であった．DIE病巣除去術に子宮全摘術を加えた症例数は11例で，すべての症例で術後骨盤痛は消失し，寛解状態となった．またDIE病巣除去術を行った妊娠希望者4例のうち3例（ART1例），DIE病巣除

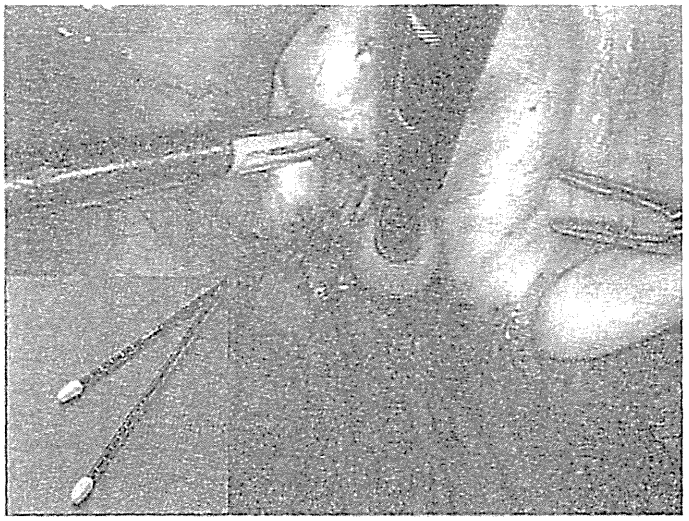

図6　ロータリーヘッドダイセクターによる癒着剝離

表1　2009年4月より3年9ヵ月間に当科で施行した子宮内膜症腹腔鏡下手術症例（230例）

年齢	36.4±8.1
r-ASRM	57.0±35.6
Douglas 窩閉鎖	83/230
DIE	72/230
稀少部位子宮内膜症	
直腸・S 状結腸	3 /230
尿管（水腎症合併）	3 /230
膀胱	4 /230
虫垂	2 /230
腟壁（後腟円蓋）	2 /230
鼠径部	2 /230

去を行わなかった妊娠希望者6例のうち3例（ART 2例）が妊娠，出産した．

考　察

子宮内膜症に対する手術の主な目的は症状改善である．子宮内膜症の主症状は疼痛と不妊であり，手術の完遂度と機能温存のバランスが肝要である．適切なDIE病巣除去術により術後の疼痛症状の改善，妊娠率の改善が得られたとする多くの報告がある〔5〕．その一方で，DIE病巣除去術により術後のARTによる妊娠率，生児獲得率の改善は得られなかったとする報告もある〔6〕．当科のデータでは，妊孕性温存手術においてDIE病巣除去術を併用した場合には高い月経痛の改善率が得られたが，短期的にはDIE病巣除去を併用しなかった症例との有意差はなかった．引き続き，より長期的あるいは多角的な疼痛改善効果の検討が求められる．またDIE病巣除去と妊娠率の改善については当科のデータでは挙児希望の症例数が少なく関連性の十分な評価ができない．さらなる症例の蓄積が必要である．

DIE病巣除去術を行うにあたり，骨盤内の系統的癒着剝離を先行させる術式とその有用性については多くの報告がある〔7〕．一方で，臓器損傷だけでなく骨盤神経叢の損傷による排尿障害を引き起こす危険性も考慮する必要がある．当科では，臓器損傷の回避のために必要に応じて直腸プローブや尿管ステントを活用するなどの工夫をしている．また剝離子に関しては吸水管，剝離鉗子，ロータリーヘッドダイセクターを剝離部位，癒着の程度により使い分け，安全性の担保に寄与している．

結　論

DIE病巣除去術の術式に関しては，正確な系統的癒着剝離と解剖学的再構築，それに引き続くDIE病巣除去，適切な剝離デバイスの選択が手術の完遂度と安全性の担保，ひいては症状改善と再発予防に寄与すると考えられた．

DIE症例に対する手術療法を遂行するにあたり，系統的癒着剝離と剝離デバイスの状況に応

じた選択が有効であると考えられた．DIE病巣除去術は，適切な系統的癒着剝離の先行により安全に施行でき，疼痛軽減に有効と考えられた．一方，DIE病巣除去術と妊孕性改善との関連性にはさらなる検討が必要と考えられた．

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ORIGINAL ARTICLE

Clinical characteristics of catamenial and non-catamenial thoracic endometriosis-related pneumothorax

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ABSTRACT

Background and objective: **A major pathogenic factor for catamenial pneumothorax is thoracic endometriosis. However, thoracic endometriosis-related pneumothorax (TERP) can develop as either catamenial or non-catamenial pneumothorax (CP). Therefore, the aim of this study was to elucidate the clinical differences between catamenial and non-catamenial TERP.**

Methods: **The clinical and pathological data in female patients who underwent video-assisted thoracoscopic surgery at the Pneumothorax Research Center during an 8-year period were retrospectively reviewed. This study included 150 female patients with surgico-pathologically confirmed TERP. The subjects were divided into two groups, those having all of the pneumothorax episodes in the catamenial period (CP group) and those who did not (non-CP group). We compared the clinical characteristics and surgico-pathological findings between these two groups.**

Results: **Of the 150 TERP patients, 55 (36.7%) were classified in the CP group, and 95 (63.3%) in the non-CP group. In regard to the locations of endometriosis, all TERP patients had diaphragmatic endometriosis, while pleural implantation was recognized in 34 of the 55 (61.8%) patients in the CP group and 42 of the 95 (44.2%) patients in the non-CP group ($P < 0.05$).**

Conclusions: **A significant difference in the proportion of patients with pleural endometriosis was observed between catamenial and non-catamenial TERP. The ectopic sites of the endometriosis may be responsible for the timing of the pneumothorax episodes.**

Key words: catamenial pneumothorax, endometriosis, pneumothorax, spontaneous pneumothorax, video assisted thoracoscopic surgery.

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SUMMARY AT A GLANCE

This study suggests that the mechanisms underlying catamenial and non-catamenial thoracic endometriosis-related pneumothorax (TERP) may be different. Pleural endometriosis has a tendency to cause catamenial TERP.

Abbreviations: CP, catamenial pneumothorax; TERP, thoracic endometriosis-related pneumothorax; VATS, video-assisted thoracoscopic surgery.

INTRODUCTION

Catamenial pneumothorax (CP) had been considered to be an unusual condition, but with increasing interest in this disease, it has been reported more frequently, and is now considered to account for 20–30% of the cases with primary spontaneous pneumothorax in females of reproductive age.[1,2] CP is generally defined simply as a recurrent pneumothorax occurring between the day before and three days after the onset of menstruation.[3,4] The pathogenesis of CP is mainly related thoracic endometriosis.[5,6] Thoracic endometriosis-related pneumothorax (TERP) is the term used to refer to a pneumothorax accompanied with thoracic endometriosis.

Until recently, TERP had been considered to manifest only as CP. However, Alifano *et al.* reported that one-third of TERP cases presented in the intermenstrual period.[7] Thus, TERP can develop as a CP as well as a non-CP. There have been only a few reports of non-catamenial TERP (the report by Alifano's group and our group), thus the clinical characteristics of non-catamenial TERP have not been clarified.[7–9] The purpose of this study was to clarify the characteristics of this condition and to speculate on the pathogenic mechanism underlying non-catamenial TERP by comparing it with catamenial TERP.

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METHODS

Study population

The clinical and pathological files of all female patients who underwent video-assisted thoracoscopic surgery (VATS) in the Pneumothorax Research Center for surgical treatment of spontaneous pneumothoraces during the 8-year period from January 2005 to December 2012 were reviewed retrospectively. All surgeries were performed as by VATS under general anaesthesia. No patients underwent thoracotomy. We included 150 females who had surgico-pathologically confirmed TERP. During surgery, we searched the thoracic cavity systematically with a thoracoscope for bullae and blebs, diaphragmatic abnormalities (holes and nodular lesions) and nodular lesions in the thoracic wall (Fig. 1). We resected the abnormalities of the diaphragm, lung and thoracic wall where endometriosis was suspected during VATS. In addition, we covered the resected areas with oxidized regenerated cellulose mesh (Surgicel Johnson and Johnson, Inc., New Brunswick, NJ, USA) to prevent any recurrence and to also reinforce the visceral pleura. The resected lesions were histopathologically confirmed as thoracic endometriosis when the endometrial glands or stroma were positively stained for estrogen/progesterone receptors or CD10.

We asked all of the patients with TERP about the temporal relationship between the pneumothorax episodes and menses to divide them into a CP group and a non-CP group. We defined the date of pneumothorax as the date of the onset of chest symptoms (chest pain, difficulty of breathing, or some respiratory discomfort). We confirmed the presence of pneumothorax by chest X-ray examinations. We carefully determined both the pneumothorax date and menstruation date by interview with the patients during each visit to our clinic. The data of the patients with recurrence after surgery were not included in the analysis. We defined the CP group as those having all of the pneumothorax episodes during the catamenial period (i.e. from the day before to within three days after the onset of menstruation[7–9]), with the remaining patients classified as the non-CP group.

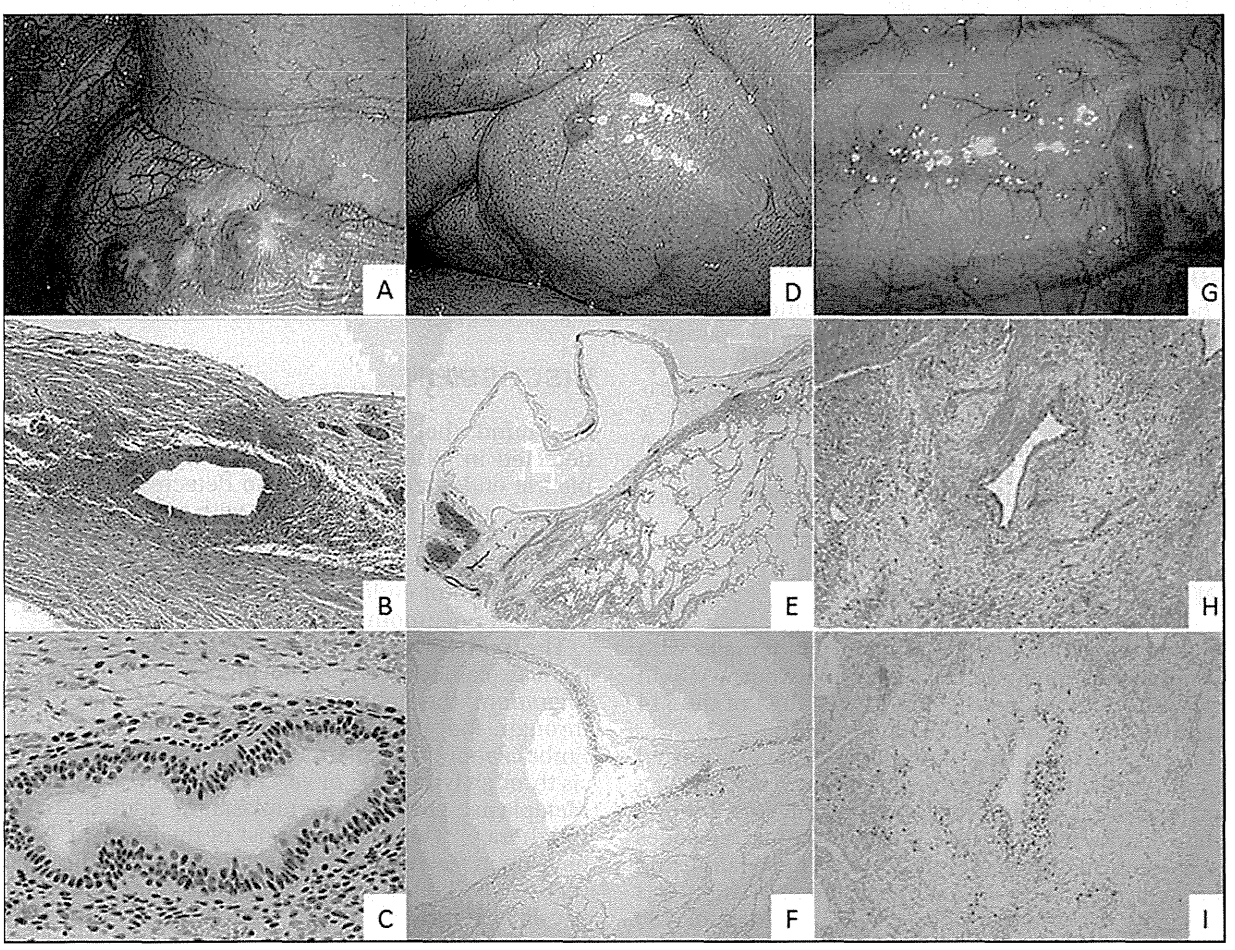

Figure 1 The thoracoscopic views of endometrial implants on the tendinous part of the right diaphragm (A), on the visceral pleura (D), and on the parietal pleura (G). Blue-brown implants (A), small bulla (D), and tiny lucent nodules (G) were detected. Endometrial glands and/or stroma were detected in the resected specimens (hematoxylin-eosin) (B, E, H). These glands and/or stroma exhibited nuclear staining for estrogen receptors (C, F, I).

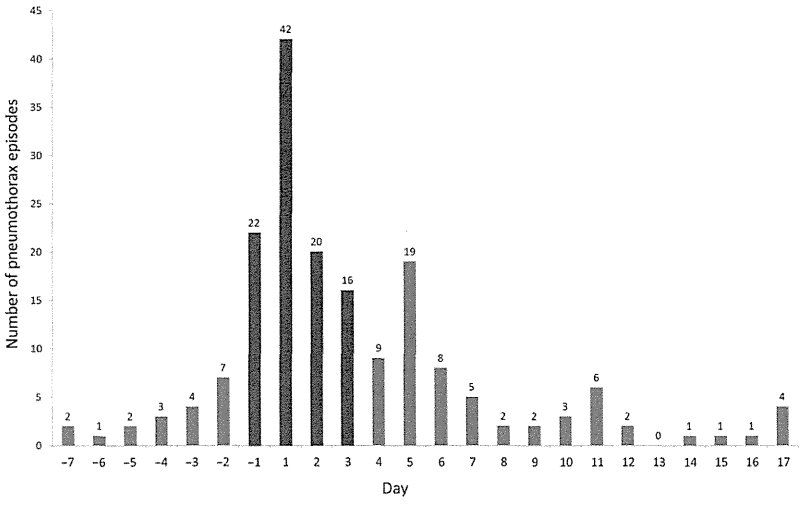

Figure 2 The distribution of pneumothorax episodes in the TERP patients. The red bars indicate catamenial pneumothorax; the pneumothorax that occurs between 24 h before and 72 h after the initiation of menses. Day 1 means the day of onset of menstruation. Day −1 means the day before the onset of menstruation.

For the patients with catamenial and non-catamenial TERP, we compared the age, pneumothorax side, height, body weight, smoking habits, history of pelvic endometriosis, value of serum CA125, number of pneumothorax episodes before surgery, duration of follow-up after surgery and the postoperative recurrence rate. Furthermore, we compared the locations of endometrial implants in the thoracic cavity between the CP and non-CP groups. The study was approved by the institutional review board of Nissan Tamagawa Hospital (approval number 14–015).

Statistical analysis

The quantitative data are presented as the means ± SD. The differences between the patients with catamenial and non-catamenial TERP were analysed using the chi-square test for categorical variables and Student's *t*-test for quantitative variables. A value of $P < 0.05$ was considered to be significant. A statistical software package (JMP version 10.0.2; SAS Institute; Cary, NC, USA) was used for the statistical analysis.

RESULTS

During the 8-year period, a total of 714 females with spontaneous pneumothoraces underwent VATS in our centre. One hundred and fifty (21.0%) of the 714 patients were diagnosed as having TERP.

A total of 570 pneumothorax episodes had occurred in the patients with TERP before the surgery, giving a mean of 3.8 ± 2.3 episodes per patient. Figure 2 shows the distribution of the pneumothorax episodes according to the menstrual cycle. The relationship between the day of episodes and menstruation was available for 288 episodes (50.5%). A total of 180 (59.4%) of the 288 episodes developed during the catamenial period.

Of the 150 patients with TERP, 55 (36.7%) were classified as the CP group, and the remainder (95/150, 63.3%) were classified as the non-CP group. Table 1 shows the clinical characteristics of each group. It should be noted that all but one of the patients developed a right-sided pneumothorax. The patients in the CP and non-CP groups showed similar clinical features.

Table 2 shows the ectopic sites of thoracic endometriosis in each group. All of the TERP patients had endometrial implants in the diaphragm. Thirty-four of the 55 (61.8%) patients in the CP group and 42 of the 95 (44.2%) patients in the non-CP group had implants not only in diaphragm, but also in the pleura. This difference was statistically significant ($P < 0.05$). Endometriosis in the visceral pleura was observed in 22 of the 55 (40%) patients in the CP group and 30 of the 95 (31.5%) patients in the non-CP group ($P = 0.30$).

DISCUSSION

We found that diaphragmatic endometriosis was detected in all of the patients with TERP, and that pleural endometriosis was also detected in some of them. As proportion of patients with endometriosis in both the diaphragm and pleura was significantly higher in the CP group than in the non-CP group, the ectopic sites of endometriosis may be related to the timing of pneumothorax episodes.

The pathogenesis of thoracic endometriosis has been explained by the following three theories: (i) Migration: the migration of pelvic endometriosis through the peritoneum to the diaphragm.[9] (ii) Embolization: transplantation of pelvic endometriosis through lymphatic or vascular embolization.[10] (iii) Metaplasia: coelomic metaplasia of epithelium in the thorax.[11] The fact that most of the cases of TERP develop in the right-side lung supports the migration theory.[12–14] The presence of intrapulmonary endometriosis supports the embolization theory.[10] Metaplasia to endometrial tissue has been reported in patients with ectopic endometriosis other than in the thorax.[11] Therefore, this phenomenon is also considered to have occurred in the thoracic cavity. In the present study, thoracic endometriosis was

Table 1 The characteristics of the study population

	Patients with TERP $n = 150$	Patients with catamenial TERP $n = 55$	Patients with non-catamenial TERP $n = 95$	*P*-value
Age (years old) (range)	38.3 ± 5.2 (24–50)	38.4 ± 4.8 (29–47)	38.3 ± 5.6 (24–50)	0.91
Side of pneumothorax				
Right	149 (99.3%)	55 (100%)	94 (98.9%)	0.45
Left	1 (0.7%)	0	1 (1.1%)	0.45
Height (cm)	159.3 ± 5.3	159.3 ± 5.4	159.3 ± 5.2	0.96
Weight (kg)	49.5 ± 5.8	50.6 ± 5.3	49.0 ± 6.0	0.10
Smoking habit				
Current/former smoker	13 (8.7%)	7 (12.7%)	6 (6.3%)	0.18
Non-smoker	137 (91.3%)	48 (87.3%)	89 (93.7%)	0.18
The number of patient with a history of pelvic endometriosis	83 (55.3%)	31 (56.4%)	52 (54.7%)	0.85
The value of serum CA125 (U/mL)	31.1 ± 34.8	29.0 ± 30.6	33.1 ± 37.8	0.51
The number of preoperative pneumothorax episodes	3.7 ± 2.4	3.4 ± 2.3	4.0 ± 2.4	0.13
Postoperative follow-up period (months)	28.4 ± 20.0	26.0 ± 18.1	29.4 ± 22.0	0.33
The number of patients with recurrence after surgery	51 (34.0%)	20 (36.4%)	31 (32.6%)	0.84

There were no missing data for any of these variables. The data are presented as number (%) or the mean ± SD. The *P*-values were calculated by comparing the patients with catamenial and non-catamenial TERP.

Table 2 The ectopic sites of thoracic endometriosis in patients with catamenial and non-catamenial TERP

	Patients with catamenial TERP $n = 55$	Patients with non-catamenial TERP $n = 95$	*P*-value
Thoracic endometriosis in the diaphragm	21 (38.2%)	53 (55.8%)	<0.05
Thoracic endometriosis in the diaphragm and pleura	34 (61.8%)	42 (44.2%)	<0.05
Thoracic endometriosis in the diaphragm and visceral pleura	16 (29.1%)	18 (18.9%)	0.15
Thoracic endometriosis in the diaphragm and parietal pleura	12 (21.8%)	12 (12.6%)	0.14
Thoracic endometriosis in the diaphragm, visceral and parietal pleura	6 (10.9%)	12 (12.6%)	0.75

All of the patients had thoracic endometriosis in the diaphragm, while some of them also had endometriosis in the pleura (visceral, parietal or both). The *P*-values were calculated by comparing the patients with catamenial and non-catamenial TERP.

observed to involve predominantly the right lung with diaphragm and pleura deposits. Recently, Legras *et al.* reported 229 female patients with pneumothoraces, including 54 TERP patients, which had a distribution of thoracic endometriosis similar to our study (53 (98.1%) had a right-sided pneumothorax, 52 (96.3%) had endometrial implants in the diaphragm and 11 (12.2%) had endometrial implants in the pleura[8]). Thus, TERP was speculated to develop largely due to the migration of pelvic endometriosis through defects in the right diaphragm. Furthermore, endometrial cells do not stay still on the diaphragm but progress to disseminate to the dorsal thoracic wall or pleura.

Our study showed that pleural endometriosis tended to occur more frequently in the CP than non-CP group. We thought that the timing of pneumothorax episodes with TERP probably varied because air from outside entered through two different passages: the transdiaphragmatic passage and transpleural passage. Endometriosis in the visceral pleura may cause a pneumothorax to occur during the early menstrual period, because the lung surface with sloughing endometriosis is directly broken.[15,16] To cause transdiaphragmatic passage, air from outside needs to overcome three different blockades: the cervix of the uterus, ovarian tubes and diaphragm.[17] All three of these are ordinarily closed, but when these blockades fail for some reason at the same time or one after another, TERP can develop in the intermenstrual period. Another possible explanation for the development of non-catamenial TERP is as follows: (i) Non-catamenial TERP may originally be a mild disease, hence the onset of chest symptoms may possibly be delayed. (ii) For the patients with pneumothorax due to the transdiaphragmatic passage of air, it seems likely that the pneumothorax developed more gradually than in patients in whom pneumothorax developed due to the transpleural passage of air, hence the date of presentation may be less precise.