

Case Report

Successful Pregnancy in Recurrent Thin Endometrium with New Uses for an Old Drug

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Abstract

Objective: To analyze whether the use of tamoxifen is a feasible option in repeated unresponsive thin endometrium (<6 mm) with standard treatment options.

Methods: Three consecutive women undergoing Frozen Embryo Transfer (FET) who, after standard endometrial preparation, still showed thin endometrium (<6 mm). They were all given with tamoxifen treatment.

Results: Successful endometrial expansion to at least 7.7 mm after tamoxifen treatment in three patients previously with thin endometrium in abandoned IVF cycles, natural cycles and extended estrogen treatment cycles with aspirin. All the three patients performed embryo-transfer, and they all conceived. One singleton stopped growing on gestational week 8. Two deliveries produced three healthy children.

Conclusion: In patients of recurrent thin endometrium, regardless of whether abandoned IVF cycles, natural cycles or extended estrogen treatment cycles with aspirin, tamoxifen treatment may be a successful alternative approach.

Keywords: Thin endometrium; Tamoxifen; Pregnancy

Introduction

Adequate growth of the endometrium is an important factor for successful implantation. Some authors have reported that there is a steady and gradual increase in pregnancy rates as endometrial thickness increases [1]. When endometrial thickness is <6 mm, the probability of achieving a full-term pregnancy decreases [2]. In order to maximize pregnancy rates, endometrial thickness from 8 mm to 14 mm was suggested [3]. There were 0.3% of patients in our center did not reach 6 mm as a thin endometrium [2]. In our center, endometrial thickness <6 mm is a criterion for fresh IVF cycle cancellation and all embryos will be cryopreserved with hoping for better endometrium growth in future Frozen Embryo Transfer (FET) cycles. However, improving endometrial growth in such patients is very difficult.

Until now, there are no standard treatment guidelines for thin endometrium in reproductive medicine. The main treatment for thin endometrium include three types: firstly, increasing serum E₂ levels, such as oral or vaginal estrogen administration [4] and low-dose HMG administration [5], extended estrogen administration [6]. Secondly, improving the uterine blood flow and treating fibrosis, such as low-dose aspirin [7], vaginal sildenafil citrate [8], pentoxifylline, vitamin E [9,10], l-arginine, sildenafil citrate [11], electroacupuncture [12], neuromuscular electrical stimulation [13]. Thirdly, using bone marrow stem/progenitor cells [14] or cytokine such as Granulocyte - Colony Stimulating Factor (G-CSF) [15] for intrauterine administration. In 2008, a review summarized that various modalities proposed for the treatment of thin endometrium seemed to be useless and inefficient from an evidence-based medicine point of view [16]. However, whether the new method of G-CSF indeed improves pregnancy chances in patients with thin endometrium remains undetermined and subject to properly designed prospectively randomized clinical trials [15]. Effective and convenient treatments are therefore still urgently needed.

We report three cases with recurrent thin endometrium <6 mm and unresponsive to maximal extended estrogen therapy. They were managed successfully with tamoxifen treatment and all conceived.

Materials and Methods

The study was reviewed and approved by the Ethical Review Board of Nanfang Hospital, Southern Medical University. Written informed consent was obtained from the three patients.

The three patients were all found to present a thin endometrium of <6 mm with a triple-line type by transvaginal ultrasound on the hCG administration day in IVF cycles. They underwent repeat observation with transvaginal ultrasound either during abandoned treatment cycles or in natural cycles after the failed attempts.

Patient 1 was 37 years old. She had a history of artificial abortion. She was diagnosed as infertility for endometriosis and pelvic adhesions. Her menses was reported to be within normal ranges, with a 26 to 30 day cycle and 4 to 5 days of bleeding. She had no history of tuberculosis. She had two cycles of intracytoplasmic sperm injection for teratozoospermia of her husband. In the first ICSI cycle, she performed embryo transfer with endometrium thinner than 6 mm, but did not conceive. In the second ICSI cycle, she asked for cryopreserving all the four embryos, hoping for better endometrium in future FET cycles. Then she had two natural cycles, two HRT cycles with aspirin 100 mg per day, one ovulation cycle with letrozole stimulation to prepare endometrium. However, the endometrial thickness did not exceed 6 mm in the 5 cycles. Then she was suggested to use 20 mg of tamoxifen for 5 days.

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Received August 23, 2013; **Accepted** September 12, 2013; **Published** September 14, 2013

Citation: Chen X, Chen SI (2013) Successful Pregnancy in Recurrent Thin Endometrium with New Uses for an Old Drug. J IVF Reprod Med Genet 1: 110. doi:10.4172/2375-4508.1000110

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Patient 2 who was a 30-year-old nulliparous patient had an IVF cycle for tubal infertility and PCOS. She had no history of uterine interventions and tuberculosis. Her endometrium was 5.0 mm in IVF cycle and embryo transfer was suggested to cancel and 9 embryos was cryopreserved. She performed embryo transfer in the subsequent HRT cycle even though the thickest endometrium was only 4.4 mm. Two compact stage embryos with 5% fragment were transferred but she did not conceive. Then she had another HRT cycle with aspirin 100 mg per day and two natural cycles to prepare endometrium, but the thickest endometrium was <6 mm in the three cycles. So we gave her one cycle with tamoxifen 20 mg per day for 5 days.

Patient 3 who was 29-year-old had a history of ectopic pregnancy. She had an IVF cycle for tubal infertility. Her endometrium was 5.0 mm on the hCG administration day in her IVF cycle and she was suggested to cancel embryo transfer. She asked for performing embryo transfer in the subsequent HRT cycle when the thickest endometrium was 6.2 mm but did not conceive. Then she had another two natural cycles and three HRT cycle with aspirin 100 mg per day to prepare endometrium, but the thickest endometrium was <6 mm in the 5 cycles. So we gave her one cycle with tamoxifen 20 mg per day for 5 days.

Results

The endometrium of patient 1 was 5.9 mm on the planned embryo transfer day in the second ICSI cycle as showed in Figure 1. The thickest endometrium and serum hormone levels in her six cycles after the

second ICSI cycle were summarized in Table 1. In the tamoxifen cycle, her endometrial thickness was 5.2, 5.7, 6.1, and 7.7 mm on 3, 6, 9, and 11 days after tamoxifen withdrawal, respectively. Her serum E₂ and LH concentrations on 6 days after tamoxifen withdrawal were 598.7 pg/mL and 11.8 mIU/mL, respectively. On 9 days after tamoxifen withdrawal, the dominant follicle was found to disappear. On 11 days after tamoxifen withdrawal, her serum E₂, LH, and P concentrations were 162 pg/mL, 8.27 mIU/mL, and 11.79 ng/mL, respectively. It was decided to warm the vitrified embryos on 12 days after tamoxifen withdrawal and transfer embryos on the next day. Both embryos were found to only one viable, and then a 6-cell embryo with 5% fragment was transferred. Eleven days after embryo transfer, serum β-hCG was found to be 171.2 mIU/mL. Two weeks later clinical heart activity was observed with transvaginal ultrasound. The gross malformation screening is normal. Currently the patient has given a birth to a healthy child.

The thickness of endometrium, the diameter of the dominant follicle and serum hormone levels in tamoxifen treatment cycle of patient 2 and patient 3 were summarized in Table 2.

The endometrial thickness of patient 2 was 6.4 mm 3 days after tamoxifen withdrawal. Seven days after tamoxifen withdrawal, her endometrial thickness was 7.8 mm and serum E₂, LH, and P concentrations were 107.0 pg/mL, 12.88 mIU/mL, and 0.492 ng/mL, respectively. No follicle sized >10 mm was observed in this cycle. Luteal phase supplement was achieved with progesterone in oil 60 mg i.m. per day from 7 days after tamoxifen withdrawal and 4 days later

Cycle		Thickest endometrium (mm)			E ₂ (pg/mL)	LH (mIU/mL)	P (ng/mL)
1	NC	5.8			216.1	13.47	0.463
2	HRT	5.7			150.8	17.55	0.560
3	NC	5.8					
4	HRT	5.5					
5	Letrozole	5.9			344	23.87	0.753
6	Tamoxifen	Days after tamoxifen withdrawal	Thickness of endometrium (mm)	The diameter of the dominant follicle (mm)			
		3	5.2	9			
		6	5.7	16	598.7	11.8	
		9	6.1	Ovulated			
		11	7.7		162	8.27	11.79

NC = Natural Cycle; HRT = Hormonal Replacement Therapy.

Table 1: The thickest endometrium and serum hormone levels by the FET cycle after the second ICSI cycle of patient 1.

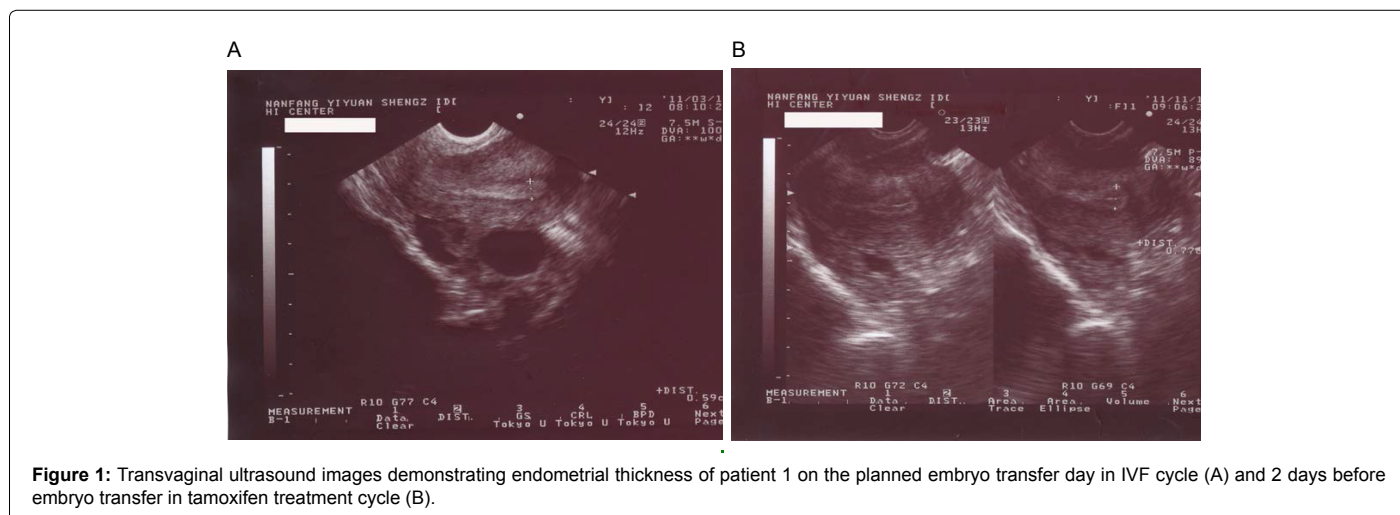


Figure 1: Transvaginal ultrasound images demonstrating endometrial thickness of patient 1 on the planned embryo transfer day in IVF cycle (A) and 2 days before embryo transfer in tamoxifen treatment cycle (B).

Patient	Days after tamoxifen withdrawal	Thickness of endometrium (mm)	The diameter of the biggest follicle (mm)	E ₂ (pg/mL)	LH (mIU/mL)	P (ng/mL)
2	3	6.4	9			
	7	7.8	8	107.0	12.88	0.492
3	2	4.3	11.5			
	6	6.1	17.5			
	8	8.1	21	794.8	105.4	1.88

Table 2: The thickness of endometrium, the diameter of the dominant follicle and serum hormone levels in tamoxifen treatment cycle of patient 2 and patient 3.

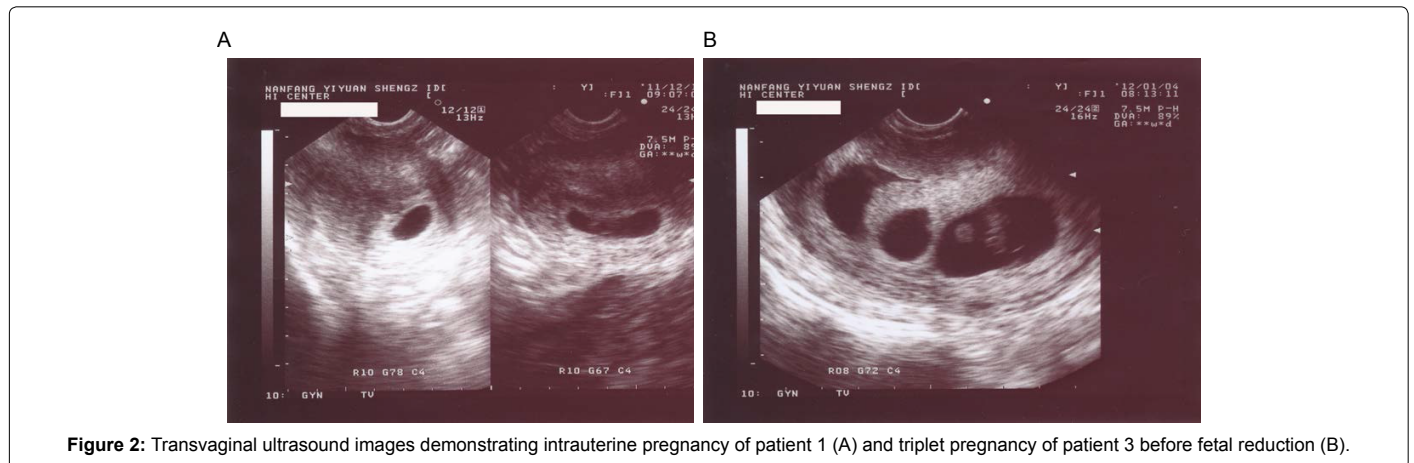


Figure 2: Transvaginal ultrasound images demonstrating intrauterine pregnancy of patient 1 (A) and triplet pregnancy of patient 3 before fetal reduction (B).

three compact stage embryos with 5% fragment were transferred. She achieved a triplet pregnancy (Figure 2). On gestational week 8 she was performed fetal reduction. Now, the patient has delivered two healthy children.

The endometrial thickness of patient 3 was 4.3, 6.1, and 8.1 mm on 2, 6, and 8 days after tamoxifen withdrawal, respectively. Her serum E₂, LH, and P concentrations on 8 days after tamoxifen withdrawal were 794.8 pg/mL, 105.4 mIU/mL, and 1.88 ng/mL, respectively. Five days later, a 10-cell embryo with 5% fragment and a 9-cell embryo with 10% fragment were transferred. Eleven days after embryo transfer, serum β-hCG was found to be 290 mIU/mL. Two weeks later clinical heart activity was observed. Unfortunately, the singleton stopped growing on gestational week 8, but villus chromosomal examination showed normal karyotype.

Discussion

We here report three IVF patients who recurred thin endometrium <6 mm in spite of extended estrogen therapy and aspirin administration in frozen embryo transfer cycles. All the three patients have experienced at least 3 other unsatisfactory alternative treatments cycles and cycles cancellation. However, they all achieved thicker endometrium than ever before with tamoxifen treatment and conceived.

Tamoxifen, the first selective estrogen receptor modulator class of drugs available for clinical use, is approved as a highly effective agent for the prevention and treatment of breast cancer. However, the long-term use of tamoxifen is associated with endometrial thickening, dysfunctional uterine bleeding, endometrial polyps, endometrial hyperplasia, and endometrial cancer [17]. Understanding the relevant molecular mechanism of tamoxifen inducing endometrial growth is important for using it properly. Some authors found that tamoxifen associated increase in total estrogen metabolites and suggested that tamoxifen increased the local estrogen biosynthesis in endometrial cells [18]. The increase in total estrogen metabolites induced by tamoxifen

could be explained with the finding that tamoxifen stimulates the GPR30 Estrogen Receptor (GPER), which in turn, activates the Steroidogenic Factor 1 (SF-1), which is a transcription factor that induces aromatase expression in endometrial cells [19]. Therefore, the proliferative action of the endometrium induced by tamoxifen is mediated, at least in part, by modulating estrogen biosynthesis and metabolism. This may in part explain the higher serum E₂ level in tamoxifen cycle (598.7 pg/mL) than any other treatment cycle of patient 1 when serum LH level was >10 mIU/mL (Table 1). However, the behaviour of tamoxifen in human endometrium is inconsistent and its particular form of agonistic profile does not completely overlap with the effect of estrogen [20]. A study has found that tamoxifen up-regulates the expression of Ki67 which is a marker of proliferation and tamoxifen also up-regulates the expression of IGF-1 [21]. Thus, the mechanism of tamoxifen increasing the endometrial thickness may include two sides: estrogen pathway and non-estrogen pathway.

Anecdotal case reports are important to establish precedents for patients' consulting service in our clinical practices and allow patients to make decisions with various treatment approaches. They also provide clues for further randomized clinical trials. Some studies have shown that the endometrial effect of tamoxifen is associated with treatment duration, cumulative dose [22] and possibly daily dose [23]. In our study, all the three patients who failed to develop thick enough endometrium of at least 6 mm with at least 3 prior cycles including natural cycles, extended estrogen treatment cycles with aspirin or letrozole stimulation cycle, but achieved significant endometrial growth and successfully conceived after 20 mg daily of tamoxifen for five days administration. These implied that 20 mg daily of tamoxifen for five days may be enough for thin endometrium treatment. However, we emphasize that this is a preliminary observational study and a final judgment on the degree to which tamoxifen treatment affects endometrial thickness awaits prospectively randomized clinical trials, these cases alone suggest that tamoxifen treatment obviously enhances endometrial thickness.

The elimination half-life of tamoxifen is 86 hours [24]. Tamoxifen is known to be metabolized to its 4-hydroxyl and N-desmethyl metabolites by the P450 enzymes. Both metabolites which are intermediate to the formation of endoxifen are considered to contribute to the effect of tamoxifen. Endoxifen was found to have a hundred fold more potent than tamoxifen with respect to estrogen receptor binding activity, while similar to that of 4-hydroxy-tamoxifen and estradiol. Prior work has shown that endoxifen concentrations are 10-fold lower than tamoxifen but 10-fold higher than 4-hydroxy-tamoxifen, indicating that it is likely to serve as a more active contributor to the antagonism of the estrogen receptor than 4-hydroxytamoxifen or even tamoxifen itself. Tamoxifen and its metabolites need more time to clear and their biological activity may retain for weeks after drug withdrawal. These may explain the persistent increase of endometrium after tamoxifen withdrawal even though patient 1 ovulated and patient 2 had no dominant follicle growing. Furthermore, review literature summarized that the majority of tamoxifen exposed infants were normal but the ascertainment of teratogenic effects from tamoxifen will best be determined by data from teratogen registries [25]. In our study, embryo transfer was performed at least 10 days after drug withdrawal. All these children are healthy.

In conclusion, when the clinician is faced with a repeat thin endometrium, the patient's status and wishes should be assessed. Clinicians should try hard to use all kinds of methods for them. Tamoxifen of 5 days administration appears to be an option that will likely result in obvious increasing thickness of endometrium and improving implantation. It may be a promising alternative for patients with thin endometrium.

Conclusion

Patients with recurrent thin endometrium achieved significant endometrial expansion after tamoxifen treatment and conceived after embryos transfer. Tamoxifen is a promising alternative for this condition.

Highlights:

- Tamoxifen is an old drug but this is a new use to treat recurrent thin endometrium.
- Patients with recurrent thin endometrium conceived after embryos transfer with tamoxifen treatment.
- This approach may improve implantation of embryos.
- The mechanism was explained.

Acknowledgments

The authors thank all of the staff at the center for their support in generating this article.

Funding

This work was supported by National Natural Science Foundation of China (81170574), Comprehensive strategic sciences cooperation projects of Guangdong Province and Chinese Academy of Sciences (2010B090301026) and Guangzhou Science and Technology Program key projects (11C22120737).

Conflict of Interest

X.C has nothing to disclose. S.-I.C has nothing to disclose

References

1. Richter KS, Bugge KR, Bromer JG, Levy MJ (2007) Relationship between endometrial thickness and embryo implantation, based on 1,294 cycles of in vitro fertilization with transfer of two blastocyst-stage embryos. *Fertil Steril* 87: 53-59.
2. Chen SL, Wu FR, Luo C, Chen X, Shi XY, et al. (2010) Combined analysis of endometrial thickness and pattern in predicting outcome of in vitro fertilization and embryo transfer: a retrospective cohort study. *Reprod Biol Endocrinol* 8: 30.
3. Lamanna G, Scioscia M, Lorusso F, Serrati G, Selvaggi LE, et al. (2008) Parabolic trend in endometrial thickness at embryo transfer in in vitro fertilization/intracytoplasmic sperm injection cases with clinical pregnancy evidence. *Fertil Steril* 90: 1272-1274.
4. Tourgeman DE, Slater CC, Stanczyk FZ, Paulson RJ (2001) Endocrine and clinical effects of micronized estradiol administered vaginally or orally. *Fertil Steril* 75: 200-202.
5. Elizur SE, Son WY, Yap R, Gidoni Y, Levin D, et al. (2009) Comparison of low-dose human menopausal gonadotropin and micronized 17beta-estradiol supplementation in in vitro maturation cycles with thin endometrial lining. *Fertil Steril* 92: 907-912.
6. Chen MJ, Yang JH, Peng FH, Chen SU, Ho HN, et al. (2006) Extended estrogen administration for women with thin endometrium in frozen-thawed in vitro fertilization programs. *J Assist Reprod Genet* 23: 337-342.
7. Weckstein LN, Jacobson A, Galen D, Hampton K, Hammel J (1997) Low-dose aspirin for oocyte donation recipients with a thin endometrium: prospective, randomized study. *Fertil Steril* 68: 927-930.
8. Sher G, Fisch JD (2000) Vaginal sildenafil (Viagra): a preliminary report of a novel method to improve uterine artery blood flow and endometrial development in patients undergoing IVF. *Hum Reprod* 15: 806-809.
9. Lédée-Bataille N, Olivennes F, Lefaix JL, Chaouat G, Frydman R, et al. (2002) Combined treatment by pentoxifylline and tocopherol for recipient women with a thin endometrium enrolled in an oocyte donation programme. *Hum Reprod* 17: 1249-1253.
10. Acharya S, Yasmin E, Balen AH (2009) The use of a combination of pentoxifylline and tocopherol in women with a thin endometrium undergoing assisted conception therapies—a report of 20 cases. *Hum Fertil (Camb)* 12: 198-203.
11. Takasaki A, Tamura H, Miwa I, Taketani T, Shimamura K, et al. (2010) Endometrial growth and uterine blood flow: a pilot study for improving endometrial thickness in the patients with a thin endometrium. *Fertil Steril* 93: 1851-1858.
12. Ho M, Huang LC, Chang YY, Chen HY, Chang WC, et al. (2009) Electroacupuncture reduces uterine artery blood flow impedance in infertile women. *Taiwan J Obstet Gynecol* 48: 148-151.
13. Bodombossou-Djobo MM, Zheng C, Chen S, Yang D (2011) Neuromuscular electrical stimulation and biofeedback therapy may improve endometrial growth for patients with thin endometrium during frozen-thawed embryo transfer: a preliminary report. *Reprod Biol Endocrinol* 25: 122.
14. Gargett CE, Healy DL (2011) Generating receptive endometrium in Asherman's syndrome. *J Hum Reprod Sci* 4: 49-52.
15. Gleicher N, Vidali A, Barad DH (2011) Successful treatment of unresponsive thin endometrium. *Fertil Steril* 95: 2123.
16. Senturk LM, Erel CT (2008) Thin endometrium in assisted reproductive technology. *Curr Opin Obstet Gynecol* 20: 221-228.
17. Cohen I (2004) Endometrial pathologies associated with postmenopausal tamoxifen treatment. *Gynecol Oncol* 94: 256-266.
18. Williams-Brown MY, Salih SM, Xu X, Veenstra TD, Saeed M, et al. (2011) The effect of tamoxifen and raloxifene on estrogen metabolism and endometrial cancer risk. *J Steroid Biochem Mol Biol* 126: 78-86.
19. Lin BC, Suzawa M, Blind RD, Tobias SC, Bulun SE, et al. (2009) Stimulating the GPR30 estrogen receptor with a novel tamoxifen analogue activates SF-1 and promotes endometrial cell proliferation. *Cancer Res* 69: 5415-5423.
20. Cano A, Hermenegildo C (2000) The endometrial effects of SERMs. *Hum Reprod Update* 6: 244-254.
21. Elkas J, Gray K, Howard L, Petit N, Pohl J, et al. (1998) The effects of tamoxifen on endometrial insulin-like growth factor-1 expression. *Obstet Gynecol* 91: 45-50.
22. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraad J, et al. (2000) Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* 356: 881-887.
23. Rutqvist LE, Johansson H, Signomkiao T, Johansson U, Fornander T, et al. (1995) Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. *J Natl Cancer Inst* 87: 645-651.

24. Hutson PR, Love RR, Havighurst TC, Rogers E, Cleary JF (2005) Effect of exemestane on tamoxifen pharmacokinetics in postmenopausal women treated for breast cancer. *Clin Cancer Res* 11: 8722-8727.
25. Berger JC, Clericuzio CL (2008) Pierre Robin sequence associated with first trimester fetal tamoxifen exposure. *Am J Med Genet A* 146A: 2141-2144.