J Korean Med Sci. 2022 Jan 10;37(2):e9
https://doi.org/10.3346/jkms.2022.37.e9
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article

Endocrinology, Nutrition & Metabolism

Association of Early Pubertal Onset in Female Rats With Inhalation of Lavender Oil

Yoo-Mi Kim [1,2] **and Han Hyuk Lim** [1,3]

[1]Department of Pediatrics, College of Medicine, Chungnam National University, Daejeon, Korea
[2]Department of Pediatrics, Chungnam National University Sejong Hospital, Sejong, Korea
[3]Department of Pediatrics, Chungnam National University Hospital, Daejeon, Korea

Received: Jul 11, 2021
Accepted: Nov 12, 2021
Published online: Dec 7, 2021

Address for Correspondence:
Yoo-Mi Kim, MD, PhD
Department of Pediatrics, Chungnam National University Sejong Hospital, 20, Bodeum 7-ro, Sejong 30099, Republic of Korea.
Email: ym4805@gmail.com

ORCID iDs
Yoo-Mi Kim
https://orcid.org/0000-0002-8440-5069
Han Hyuk Lim
https://orcid.org/0000-0002-5297-5913

Funding
This work was supported by the Chungnam National University (grant No. 2019-0522-01).

Disclosure
The authors have no potential conflicts of interest to disclose.

Author Contributions
Conceptualization: Kim YM. Data curation: Kim YM. Formal analysis: Kim YM. Investigation: Kim YM. Writing - original draft: Kim YM, Lim HH. Writing - review & editing: Kim YM, Lim HH.

ABSTRACT

Background: Central precocious puberty (CPP) is caused by early activation of the hypothalamic–pituitary–gonadal axis but its major cause remains unclear. Studies have indicated an association between chronic environmental exposure to endocrine-disrupting chemicals and pubertal onset. Essential oil is widely used in homes worldwide for relief of respiratory symptoms, stress, and/or sleep disturbance.
Methods: To evaluate this association, we compared the hormone levels and timing of vaginal opening (VO) in female rats exposed to lavender oil (LO) through different routes (study groups: control, LO nasal spray [LS], and indoor exposure to LO [LE]) during the prepubertal period. The body weights of the animals were also compared every 3 days until the day of VO, at which time gonadotropin levels and internal organ weights were assessed.
Results: The LS group showed early VO at 33.8 ± 1.8 days compared with the control (38.4 ± 2.9 days) and LE (36.6 ± 1.5 days) groups. Additionally, luteinizing hormone levels were significantly higher in the LE and LS groups than those in the control group. Body weights did not differ significantly among the groups.
Conclusion: Inhalation exposure to an exogenic simulant during the prepubertal period might trigger early pubertal onset in female rats. Further evaluation of exposure to other endocrine-disrupting chemicals capable of inducing CPP through the skin, orally, and/or nasally is warranted.

Keywords: Precocious Puberty; Endocrine Disruptors; Lavender Oil; Inhalation Exposure; Vaginal Opening

INTRODUCTION

Central precocious puberty (CPP) describes the early activation of the hypothalamic–pituitary–gonadal (HPG) axis, which leads to the rapid progression of bone age, early menarche, reduction in final adult height, and the appearance of secondary sexual characteristics before 8 and 9 years of age in girls and boys, respectively.[1] Traditionally, CPP is accompanied by intracranial lesions, including optic glioma, pilocytic astrocytoma, hydrocephalus, Rathke's cleft cyst, and pituitary adenomas, in 40–90% of boys and < 10% of girls.[2,3] The gonadotropin-releasing hormone (GnRH) stimulation test is used for diagnosing

CPP, and the basal luteinizing hormone (LH) level is considered as a valuable tool to assess pubertal state.[4] CPP treatment was introduced in 1980, and dosing of a recombinant GnRH agonist every 4 weeks or 3 months leads to increases in the final adult height and delayed menarche.[2,3] Improving the final adult height of children with CPP is one of the major issues during treatment.[5,6] However, the incidence of precocious puberty is rapidly increasing, and examination and treatment of this condition are becoming a major burden because of the associated medical expenses, although the cause of this condition remains unknown.[2,3]

Environmental hormones, i.e., endocrine-disrupting chemicals, were recently suggested to contribute to the onset of puberty in childhood,[7,8] and animal studies demonstrated that endocrine-disrupting chemicals accelerate pubertal onset.[9,10] Additionally, previous reports showed that lavender oil (LO) and tea tree oil are associated with prepubertal gynecomastia in boys.[11,12] Moreover, cases of premature thelarche that resolved after cessation of exposure to lavender-containing fragrance have been reported,[13,14] and an in vitro study showed that components of LO, including linalool and linalyl acetate, activate estrogen-related gene expression in human cell lines.[13] However, studies of the absorbance of these materials in sufficient amounts and their effect on breast growth have not been performed. A previous study suggested that smell of sense can be transmitted to the central nervous system, thereby facilitating the bypass of inhaled molecules via the nasal pathway of the blood–brain barrier.[15] There are several opportunities for inhalation of numerous endocrine-disrupting chemicals from estrogenic sources in cosmetics, perfumes, air fresheners, and scented candles/diffusers using essential oils, which can directly affect olfactory stimulation of the neuroendocrine system. Since some studies suggested that essential oils may have efficacy against the coronavirus disease 2019 and its inflammatory complications,[16-18] the interests for home therapy using essential oils are more increasing.

In this study, we tested whether continuous inhalation of LO affects early gonadotropin activation and precocious puberty. However, it is difficult to limit or measure the number of EDCs to nasal exposure in human. Thus, we investigated the effects of continuous inhalation of LO on pubertal onset and gonadotropin hormone levels in an animal model and compared them to control conditions.

METHODS

Animals and experimental design

To obtain study animals, rats were bred using male and female Sprague–Dawley rats. From birth onward, we maintained an indoor temperature of 22°C (humidity: 30–70%) and controlled illumination (12-hour light/dark cycle) to allow breeding in a constant environment along with free access to water and food. On day 18 after birth, we identified 15 immature females and randomly divided them into three groups: olfactory stimulation groups 1 and 2 and a control group (n = 5/group). We used 100% pure LO obtained from *Lavandula angustifolia* (NOW Foods, Bloomingdale, IL, USA) for all experiments. Group 1 was treated by indoor exposure to LO (LE) via an LO diffuser in the cage using an LO-soaked puff (changed daily) along with daily exposure to 0.9% NaCl spray. For Group 2, LO was administered as a nasal spray of aromatic LO (LS) once daily. The control group was treated with a single exposure to a nasal spray (0.9% NaCl) daily. The dose of one spray of LO or 0.9% NaCl ranged from 72–125 μL. The body weight of the animals was measured every 3 days from postnatal day (PND) 18 to the day of vaginal opening (VO).

https://doi.org/10.3346/jkms.2022.37.e9

Analysis of VO

All study groups were evaluated for VO time as an indicator of pubertal initiation at a fixed time (09:00 hour) daily. The day of VO was recorded, and VO timing was compared between the three study groups.

Euthanasia and hormone assays

After VO was observed in each rat, we measured serum LH, follicle-stimulating hormone (FSH), and estradiol levels to compare hormone concentrations between study groups. The endpoint of the experiment was defined as VO occurring in the last rat. For this process, truncal blood was collected into ice-cold ethylenediamine tetraacetic acid-containing tubes after decapitation, after which the tubes were centrifuged, and plasma samples were collected and stored at −20°C until analysis. The plasma levels of LH, FSH, and estradiol of each rat were measured using enzyme-linked immunosorbent assay kits (cat. No. MBS764675, MBS2502190, and MBS263850, respectively; MyBioSource, Inc., San Diego, CA, USA) according to manufacturer's instructions.

Measurement of organ weight

After euthanasia, we measured the weight of the ovaries, spleen, kidneys, and liver. The organ weight was then modified by body weight and presented as tissue weight per 150 g body weight.

Statistical analysis

Data were presented as the mean ± standard deviation, and statistical analyses were performed using SPSS software (v.26.0; SPSS, Inc., Chicago, IL, USA). Statistical significance was determined by Kruskal-Wallis test and one-way analysis of variance for multiple-group comparisons and Mann-Whitney U test for comparisons between two groups. Statistical significance was defined at $P < 0.05$.

Ethics statement

The procedures used and the care of animals were approved by the Institutional Animal Care and Use Committee in Southwest Medi-Chem Institute (approval No. SEMI-20-001).

RESULTS

Effect of olfactory exposure to LO on VO and pubertal onset

VO occurred earlier in the LE (33.8 ± 1.8 days) and LS (36.6 ± 1.5 days) groups than in the control group (38.4 ± 2.9 days) (**Table 1**), and VO in the LE group occurred significantly earlier than in the control group ($P = 0.014$) and LS group ($P = 0.032$), respectively. However, there

Table 1. Comparison of vaginal opening day among different study groups

Group	VO (age, days)		
	Control	LS	LE
Rat			
1	41	37	37
2	41	37	33
3	38	34	33
4	38	37	33
5	34	38	33
Mean ± SD	38.4 ± 2.9	36.6 ± 1.5	33.8 ± 1.8*,**

LS = exposure to lavender oil as a nasal spray, LE = exposure to diffused lavender oil, VO = vaginal opening.
*$P < 0.05$ vs. control; **$P < 0.05$ vs. LS group.

https://doi.org/10.3346/jkms.2022.37.e9

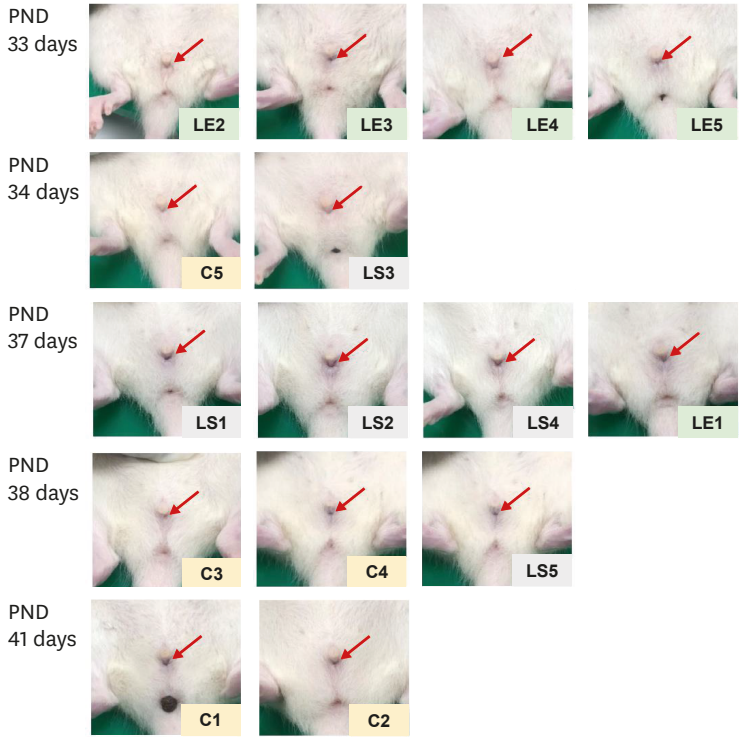

Fig. 1. Different vaginal opening onset times according to olfactory exposure to lavender oil.
PND = postnatal day, LE = exposure to diffused lavender oil, C = control, LS = exposure to lavender oil as a nasal spray.

was no significant difference between the LS and control groups with respect to VO timing (P = 0.151). Almost all rats in the LE group experienced VO at 33 days, and the control group mostly showed VO between 38 and 41 days (**Fig. 1**).

Measurement of gonadotropin hormone and estradiol levels

LH levels were significantly higher in the LE (67.6 ± 3.0 mIU/mL) and LS (64.3 ± 7.4 mIU/mL) groups than in the control group (49.9 ± 2.7 mIU/mL; P < 0.001 for both) (**Table 2**). Additionally, FSH levels were significantly higher in the LE (50.9 ± 9.1 ng/mL) and LS (51.4 ± 7.1 ng/mL) groups than in the control group (35.2 ± 3.7 ng/mL; P = 0.009 and P = 0.011, respectively). Estradiol levels were elevated in both the LE (4.9 ± 1.4 ng/mL) and LS (5.3 ± 1.4 ng/mL) groups relative to the control group (3.9 ± 0.8 ng/mL), although the differences were not significant (P = 0.326 and P = 0.547, respectively).

Table 2. Comparison of hormone levels among different study groups

Hormones	Control	LS	LE
LH, mIU/mL	49.9 ± 2.7	64.3 ± 7.4**	67.6 ± 3.0**
FSH, ng/mL	35.2 ± 3.7	51.4 ± 7.1*	50.9 ± 9.1*
Estradiol, ng/mL	3.9 ± 0.8	5.3 ± 1.4[a]	4.9 ± 1.4[a]

Data are presented as the mean ± SD (n = 5).
LH = luteinizing hormone, FSH = follicle-stimulating hormone, LS = exposure to lavender oil as a nasal spray, LE = exposure to diffused lavender oil.
[a]Not significant vs. control.
*P < 0.05 vs. control; **P < 0.001 vs. control.

https://doi.org/10.3346/jkms.2022.37.e9

Table 3. Comparison of average body weights of female rats among three groups on different PNDs

PND	Control	LS	LE
21	43.8 ± 2.6[a] g	44.0 ± 3.1 g	41.6 ± 1.7 g
27	76.6 ± 4.6[a] g	75.6 ± 3.6 g	72.5 ± 2.8 g
33	115.4 ± 7.6[a] g	110.2 ± 4.9 g	110.8 ± 5.7 g

Data are presented as the mean ± SD (n = 5).
PND = postnatal day, LS = exposure to lavender oil as a nasal spray, LE = exposure to diffused lavender oil.
[a]Not significant.

Table 4. Comparison of organ weights of female rats among three groups

Organ[a]	Control	LS	LE
Liver	7.658 ± 0.276[b]	7.642 ± 0.175	7.778 ± 0.346
Spleen	0.570 ± 0.046[b]	0.579 ± 0.064	0.639 ± 0.119
Kidney	1.664 ± 0.077	1.694 ± 0.154	1.926 ± 0.154[*,**]
Ovary	0.326 ± 0.054[b]	0.321 ± 0.043	0.368 ± 0.038

Data are presented as the mean ± SD (n = 5).
LS = exposure to lavender oil as a nasal spray, LE = exposure to diffused lavender oil.
[a]Tissue weight (g) per body weight (150 g); [b]Not significant.
[*]$P < 0.01$ vs. control; [**]$P < 0.05$ vs. LS group.

Measurement of body and organ weights

Measurement of the body weight of rats in the control, LE, and LS groups every 3 days from PND 18 until VO revealed no significant differences among three groups (**Fig. 2** and **Table 3**). The weights of the ovaries, liver, and spleen after VO showed no significant differences among three groups; however, the weight of the kidneys per 150 g body weight increased significantly after VO in the LE group (1.926 ± 0.154 g) compared with that in the control (1.664 ± 0.077 g; $P = 0.009$) and LS (1.694 ± 0.154 g; $P = 0.017$) groups (**Table 4**).

DISCUSSION

In this study, we found that persistent exposure to LO is associated with the HPG axis activation and early pubertal onset. We observed early VO in rats persistently exposed to LO as compared with that in the control group.

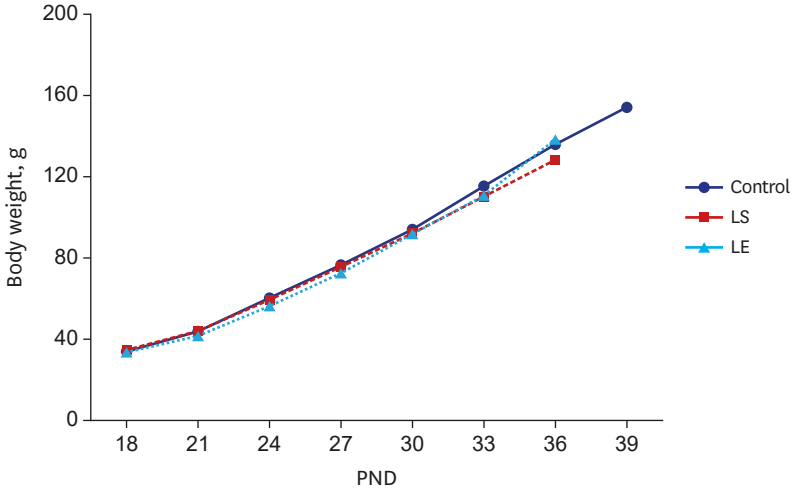

Fig. 2. Changes in mean body weight from PND 18 and after lavender oil exposure.
PND = postnatal day, LS = exposure to lavender oil as a nasal spray, LE = exposure to diffused lavender oil.

https://doi.org/10.3346/jkms.2022.37.e9

VO in the Sprague-Dawley rats occurs after the surge of gonadotropins ranges from PND 30.8 to 38.4, and it might be affected by the environment, nutrition, temperature, and light.[19-21] In a controlled environment, the mean VO of the control group in this study was 38.4 days, and VO occurred significantly earlier in the LE group (33.8 days).

Additionally, serum LH and FSH levels were significantly higher in the LE and LS groups than in the control group. The LH level has been considered as a golden marker of pubertal status, whereas the estradiol level showed a fluctuation during the day and could be low even in the pubertal period.[22-25] Chronic and persistent exposure to estrogens could also affect gonadotropin activation. Chronic exposure to sex hormone in cases of peripheral precocious puberty, including congenital adrenal hyperplasia or McCune-Albright syndrome, could lead to the secondary CPP, and these patients require to be treated with the GnRH agonist.[26,27]

Previous studies showed that estrogenic effect of LO affected the premature thelarche in girls and gynecomastia in boys.[11-14] To the best of our knowledge, no previous studies have reported an association between pubertal onset and persistent olfactory exposure to LO in an animal model. Nasal inhalation is an important source of iatrogenic sex-hormone exposure, and olfactory exposure to LO may result in LO delivery to the central nervous system and bloodstream to induce an iatrogenic effect of estrogen.

Several studies have shown that LO is effective at reducing menopausal symptoms and supporting healthy sleep.[28,29] Additionally, previous studies reported that LO does not increase estrogen levels in adults[30]; in contrast, in the present study, we could not conclude that LO exposure did not affect estrogen activity. Although we observed no differences in estradiol levels between the LE and control groups, the LE group showed early pubertal onset and significantly increased LH and FSH levels. Furthermore, the LS group showed no significant differences in VO compared with the control group. Therefore, the amount and persistence of LO exposure may determine pubertal onset.

A previous animal study reported that percutaneous injection of LO when performing uterotrophic assays on immature rats results in significantly reduced body weight gain after 3 days compared with that in the control group and a group administered 17α-ethinyl estradiol.[31] However, the authors only assessed weight gain and organ-weight-to-terminal-body-weight to evaluate the presence of an estrogenic effect, and did not compare hormone levels or VO timing. The different administration modalities may have been responsible for the reported differences in body weight gain between the LO injection group and the group undergoing oral estrogen administration. In the present study, we found no differences in organ weight, including the ovaries, and body weight gain between groups, despite the apparently different VO and gonadotropin levels. Interestingly, the kidney tissue weight was significantly increased only in the LE group, supporting an association between physiological LO-specific effects and endocrine effects. A recent study showed that LO exposure affects renal restoration in a dose-dependent manner by decreasing antioxidant signals and inflammatory cytokine levels, as well as by inhibiting apoptosis.[32] In the present study, we measured neither renal function nor nephron numbers and used only renal tissue weight as an indicator of the positive effect of LO exposure. Therefore, increased renal tissue weight may indicate a renal burden related to LO excretion.

Four studies have reported a total of 11 pediatric patients (seven males and four females) showing premature thelarche in females (age range: 14 months to 7 years and 9 months) and

gynecomastia in males (age range: 4 years and 5 months to 10 years and 1 month) after using an LO-containing product.[11-14] Ramsey et al.[13] reported that patients showed symptomatic improvement after discontinuation of LO exposure accompanied by no abnormal laboratory findings. These reports suggest the estrogenic effect of topical preparation of LO. Additionally, in vitro studies showed that LO (or the LO components linalool and linalyl acetate) exerts an estrogenic effect by stimulating α-transcription of the estrogen receptor.[11,13] The peripheral hormones or signals transmitting to GnRH neurons may lead to GnRH secretion and stimulation of pituitary gonadotropins and gonadal sex steroids.[8] Given our observation of early activation of the HPG axis after olfactory exposure to LO, further investigation of the effect of LO on gene activation related to GnRH synthesis or secretion may explain the associations between early activation of the HPG axis and LO exposure.

We focused on the effects of LO exposure through olfactory stimulation and not via oral ingestion or topical application. One limitation of this study is its small sample size; thus, further studies are required to validate the findings. We observed significant elevation of gonadotropin levels not only in the LE group but also in the LS group, suggesting that repetitive olfactory exposure affected the manifestation of LO-specific physiological effects. Several studies reported that essential LO affects anxiety when administered via the oral or nasal routes.[33-35] However, LO exposure via oral ingestion in food is not as common as skin absorption of various LO-containing cosmetic products or LO inhalation. Nevertheless, inhalation of environmental LO is difficult to quantify in humans, and epidemiological surveillance data for the sole effect of LO inhalation in children undergoing precocious puberty are unavailable. Furthermore, the frequency and duration of exposure to LO inhalation are highly variable, and the effect of LO following skin exposure on children remains inconclusive because of the variable amounts of LO to which the skin is exposed, and difficulties associated with follow-up to assess long-term effects.[36]

This study showed the effect of olfactory stimulation by LO on the early onset of puberty. These results suggest that avoidance of LO exposure to minimize unnecessary iatrogenic estrogen effects from fragrances, diffusers, and perfumes can prevent early stimulation of the HPG axis, particularly in younger children. Further in vitro evaluation of LO-related effects on central kisspeptin signaling may reveal the mechanisms associated with early activation of the HPG axis by persistent olfactory exposure to LO.

ACKNOWLEDGMENTS

We would like to thank the Southwest Medi-Chem Institute's support for animal experiment.

REFERENCES

1. Phillip M, Lazar L. Precocious puberty: growth and genetics. *Horm Res* 2005;64 Suppl 2:56-61.
PUBMED | CROSSREF
2. Fuqua JS. Treatment and outcomes of precocious puberty: an update. *J Clin Endocrinol Metab* 2013;98(6):2198-207.
PUBMED | CROSSREF
3. Carel JC, Léger J. Clinical practice. Precocious puberty. *N Engl J Med* 2008;358(22):2366-77.
PUBMED | CROSSREF

4. Ab Rahim SN, Omar J, Tuan Ismail TS. Gonadotropin-releasing hormone stimulation test and diagnostic cutoff in precocious puberty: a mini review. *Ann Pediatr Endocrinol Metab* 2020;25(3):152-5.
PUBMED | CROSSREF
5. Kim MS, Koh HJ, Lee GY, Kang DH, Kim SY. Comparing adult height gain and menarcheal age between girls with central precocious puberty treated with gonadotropin-releasing hormone agonist alone and those treated with combined growth hormone therapy. *Ann Pediatr Endocrinol Metab* 2019;24(2):116-23.
PUBMED | CROSSREF
6. Cho AY, Ko SY, Lee JH, Kim EY. Relationship between final adult height and birth weight after gonadotropin-releasing hormone agonist treatment in girls with central precocious puberty. *Ann Pediatr Endocrinol Metab* 2020;25(1):24-30.
PUBMED | CROSSREF
7. Lee JE, Jung HW, Lee YJ, Lee YA. Early-life exposure to endocrine-disrupting chemicals and pubertal development in girls. *Ann Pediatr Endocrinol Metab* 2019;24(2):78-91.
PUBMED | CROSSREF
8. Abreu AP, Kaiser UB. Pubertal development and regulation. *Lancet Diabetes Endocrinol* 2016;4(3):254-64.
PUBMED | CROSSREF
9. Yang R, Wang YM, Zhang L, Zhao ZM, Zhao J, Peng SQ. Prepubertal exposure to an oestrogenic mycotoxin zearalenone induces central precocious puberty in immature female rats through the mechanism of premature activation of hypothalamic kisspeptin-GPR54 signaling. *Mol Cell Endocrinol* 2016;437:62-74.
PUBMED | CROSSREF
10. Kriszt R, Winkler Z, Polyák Á, Kuti D, Molnár C, Hrabovszky E, et al. Xenoestrogens ethinyl estradiol and zearalenone cause precocious puberty in female rats via central kisspeptin signaling. *Endocrinology* 2015;156(11):3996-4007.
PUBMED | CROSSREF
11. Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. *N Engl J Med* 2007;356(5):479-85.
PUBMED | CROSSREF
12. Diaz A, Luque L, Badar Z, Kornic S, Danon M. Prepubertal gynecomastia and chronic lavender exposure: report of three cases. *J Pediatr Endocrinol Metab* 2016;29(1):103-7.
PUBMED | CROSSREF
13. Ramsey JT, Li Y, Arao Y, Naidu A, Coons LA, Diaz A, et al. Lavender products associated with premature thelarche and prepubertal gynecomastia: case reports and endocrine-disrupting chemical activities. *J Clin Endocrinol Metab* 2019;104(11):5393-405.
PUBMED | CROSSREF
14. Linklater A, Hewitt JK. Premature thelarche in the setting of high lavender oil exposure. *J Paediatr Child Health* 2015;51(2):235.
PUBMED | CROSSREF
15. Kentner AC, Scalia S, Shin J, Migliore MM, Rondón-Ortiz AN. Targeted sensory enrichment interventions protect against behavioral and neuroendocrine consequences of early life stress. *Psychoneuroendocrinology* 2018;98:74-85.
PUBMED | CROSSREF
16. Valussi M, Antonelli M, Donelli D, Firenzuoli F. Appropriate use of essential oils and their components in the management of upper respiratory tract symptoms in patients with COVID-19. *J Herb Med* 2021;28:100451.
PUBMED | CROSSREF
17. Silva JKRD, Figueiredo PLB, Byler KG, Setzer WN. Essential oils as antiviral agents. Potential of essential oils to treat SARS-CoV-2 infection: an in-silico investigation. *Int J Mol Sci* 2020;21(10):3426.
PUBMED | CROSSREF
18. Wilkin PJ, Al-Yozbaki M, George A, Gupta GK, Wilson CM. The undiscovered potential of essential oils for treating SARS-CoV-2 (COVID-19). *Curr Pharm Des* 2020;26(41):5261-77.
PUBMED | CROSSREF
19. Beckman DA, Feuston M. Landmarks in the development of the female reproductive system. *Birth Defects Res B Dev Reprod Toxicol* 2003;68(2):137-43.
PUBMED | CROSSREF
20. Beck MJ, Padgett EL, Bowman CJ, Wilson DT, Kaufman LE, Varsho BJ, et al. Nonclinical juvenile toxicity testing. In: Hood R, editor. *Developmental and Reproductive Toxicity: a Practical Approach*. 2nd ed. Boca Raton, FL, USA: Taylor & Francis Group; 2006, 308-9.
21. Rivest RW. Sexual maturation in female rats: hereditary, developmental and environmental aspects. *Experientia* 1991;47(10):1027-38.
PUBMED | CROSSREF

22. Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. *Pediatrics* 2009;123(6):e1059-63.
PUBMED | CROSSREF

23. Sehested A, Juul AA, Andersson AM, Petersen JH, Jensen TK, Müller J, et al. Serum inhibin A and inhibin B in healthy prepubertal, pubertal, and adolescent girls and adult women: relation to age, stage of puberty, menstrual cycle, follicle-stimulating hormone, luteinizing hormone, and estradiol levels. *J Clin Endocrinol Metab* 2000;85(4):1634-40.
PUBMED | CROSSREF

24. Sims EK, Addo OY, Gollenberg AL, Himes JH, Hediger ML, Lee PA. Inhibin B and luteinizing hormone levels in girls aged 6–11 years from NHANES III, 1988–1994. *Clin Endocrinol (Oxf)* 2012;77(4):555-63.
PUBMED | CROSSREF

25. DiVall SA, Radovick S. Pubertal development and menarche. *Ann N Y Acad Sci* 2008;1135(1):19-28.
PUBMED | CROSSREF

26. Partsch CJ, Sippell WG. Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens. *Hum Reprod Update* 2001;7(3):292-302.
PUBMED | CROSSREF

27. Eugster EA. Update on precocious puberty in girls. *J Pediatr Adolesc Gynecol* 2019;32(5):455-9.
PUBMED | CROSSREF

28. Salehi-Pourmehr H, Ostadrahimi A, Ebrahimpour-Mirzarezaei M, Farshbaf-Khalili A. Does aromatherapy with lavender affect physical and psychological symptoms of menopausal women? A systematic review and meta-analysis. *Complement Ther Clin Pract* 2020;39:101150.
PUBMED | CROSSREF

29. Bakhtiari S, Paki S, Khalili A, Baradaranfard F, Mosleh S, Jokar M. Effect of lavender aromatherapy through inhalation on quality of life among postmenopausal women covered by a governmental health center in Isfahan, Iran: a single-blind clinical trial. *Complement Ther Clin Pract* 2019;34:46-50.
PUBMED | CROSSREF

30. Shinohara K, Doi H, Kumagai C, Sawano E, Tarumi W. Effects of essential oil exposure on salivary estrogen concentration in perimenopausal women. *Neuroendocrinol Lett* 2017;37(8):567-72.
PUBMED

31. Politano VT, McGinty D, Lewis EM, Hoberman AM, Christian MS, Diener RM, et al. Uterotrophic assay of percutaneous lavender oil in immature female rats. *Int J Toxicol* 2013;32(2):123-9.
PUBMED | CROSSREF

32. Aboutaleb N, Jamali H, Abolhasani M, Pazoki Toroudi H. Lavender oil (*Lavandula angustifolia*) attenuates renal ischemia/reperfusion injury in rats through suppression of inflammation, oxidative stress and apoptosis. *Biomed Pharmacother* 2019;110:9-19.
PUBMED | CROSSREF

33. Bradley BF, Brown SL, Chu S, Lea RW. Effects of orally administered lavender essential oil on responses to anxiety-provoking film clips. *Hum Psychopharmacol* 2009;24(4):319-30.
PUBMED | CROSSREF

34. Donelli D, Antonelli M, Bellinazzi C, Gensini GF, Firenzuoli F. Effects of lavender on anxiety: a systematic review and meta-analysis. *Phytomedicine* 2019;65:153099.
PUBMED | CROSSREF

35. Karan NB. Influence of lavender oil inhalation on vital signs and anxiety: a randomized clinical trial. *Physiol Behav* 2019;211:112676.
PUBMED | CROSSREF

36. Hawkins J, Hires C, Dunne E, Baker C. The relationship between lavender and tea tree essential oils and pediatric endocrine disorders: a systematic review of the literature. *Complement Ther Med* 2020;49:102288.
PUBMED | CROSSREF