Received: 13 August 2022 | Revised: 1 September 2022 | Accepted: 7 September 2022

DOI: 10.1111/dth.15811

DERMATOLOGIC THERAPY WILEY

ORIGINAL ARTICLE

Systemic isotretinoin for acne treatment: Ovarian reserve is safe with the low dose

Asmaa M. Haroun[1] | Menha A. Ibrahim[1] | Ahmed S. Soliman[2] | Amira O. Abdel-Ghaffar[3] | Ghada M. Shams[1]

[1]Department of Dermatology, Venereology and Andrology, Benha University, Banha, Egypt

[2]Department of Gynecology and Obstetrics, Benha University, Banha, Egypt

[3]Department of Clinical and Chemical Pathology, Benha University, Banha, Egypt

Correspondence
Ghada M. Shams, Department of Dermatology, Venereology and Andrology, Benha University, Banha, Egypt.
Email: ghadashams84@gmail.com

Abstract

Isotretinoin is among the most frequently used medications in the dermatologic daily practice. With a Black box warning, teratogenicity is a major concern. Female fertility may be an issue to be investigated when it comes to its use in females. The aim of this work was to assess the effect of low dose isotretinoin on the ovarian reserve in female patients with moderate to severe acne. Sixty-sex female acne patients candidate for isotretinoin therapy and 66 controls were enrolled in this prospective controlled cohort study. Low dose isotretinoin (0.25–0.4 mg/kg/day) was given to the patients group for 6 months. Serum anti-Mullarian hormone (AMH), ovarian volume (OV) and Antral follicle count (AFC) were evaluated at baseline and 6 months after the last dose in the patients' group, and 1 year after the baseline assessment for the control subjects. There was no significant difference in serum AMH between patients after isotretinoin treatment and control subjects ($p = 0.898$). AMH failed to show any significant change in pre- and post- treatment levels in patients' group ($p = 0.747$). Both OV and AFC showed no significant changes in patient group when comparing pre- post- treatment levels on both sides ($p > 0.05$) and in control group between baseline and 1-year-interval levels on both sides ($p > 0.05$). Low-dose isotretinoin in treatment of moderate to severe acne seems to be safer on ovarian reserve as indicated by non-significant change in AMH levels as a sensitive parameter of female fertility.

KEYWORDS
acne, anti mullerian hormone, antral follicle count, isotretinoin, ovarian reserve

1 | INTRODUCTION

Since first approved by the US Food and Drug Administration (FDA) in 1982 to treat severe, resistant, and nodular acne, oral isotretinoin (13-*cis*-retnoic acid) has revolutionized the therapeutic plans and outcome of acne treatment. Off-label uses continue to emerge thereafter.

The side effects of isotretinoin range from tolerable, including dry skin and mucous membranes, to moderate like arthralgia and temporary elevated liver enzymes. Troublesome side effects may include hypertriglyceridemia, mental depression, or even suicidal attempts.[1]

Retinoids pronounced teratogenic effects have previously been reported in animal studies, and they were officially confirmed in humans in 1983.[2] Nowadays, they are considered the most teratogenic medications after thalidomide.[3]

Sebocyte apoptosis is triggered by isotretinoin-induced production of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), insulin-like growth factor binding protein-3 (IGFBP3), and neutrophil gelatinase-associated lipocalin (NGAL), which suppresses sebum.[4] Not only apoptosis may have a role in the drug's principal mode of action, but it could also be the cause of majority of isotretinoin's side effects.

The build-up of apoptotic pro-proteins is thought to participate in the apoptosis of neural crest cells and the emergence of malformations and could also lead to ovarian reserve (OR) impairment.[4] Fertility is indicated by OR by demonstrating oocyte quality and the density of the primordial follicle pool.[5]

Anti- Müllarian hormone (AMH), secreted by granulosa cells of the newly growing follicles, has been investigated to serve as a good indicator of OR.[6]

Taking into consideration that isotretinoin is also a known chemotherapeutic medication used in treatment of certain types of tumors including leukemias,[7] we thought that its effect on fertility, especially depletion of OR, like other chemotherapeutic agents, should be the next field of research.

2 | METHODS AND MATERIALS

The protocol for this prospective controlled cohort study was approved by the local Research Ethics Committee (MS:31-7-2019) in accordance with the principles of the Helsinki Declaration. Patients were selected from vulnerable population, and informed consents were obtained from all participants. Personal privacy was protected at all levels. The information gathered has not been used for any other purpose.

The study, performed during the period from October 2020 to October 2021, included 66 female acne patients (20–37 years old) candidates for isotretinoin therapy and 66 age-matched (19–35 years old) apparently healthy control subjects. Female patients suffering from variant degrees of acne, not receiving systemic treatment for acne for at least 1 month, with regular menstrual cycles and normal ovarian morphology confirmed by ultrasonography were indulged in the study. Pregnant and lactating females were not included.

Normal lipid profile and 2 negative pregnancy tests in married subjects (the last of which is done 19 days after the first negative pregnancy test and within the first 5 days of the patient's menstrual cycle) were prerequisites for isotretinoin therapy. Married patients were advised to use two methods of birth control (apart from hormonal methods) during the study period and 1 month after the last isotretinoin dose.

Patients with any systemic disease (hypertension, thromboembolic events, diabetes mellitus, cardiovascular problems, strokes, Cushing's disease, cancer, congenital adrenal hyperplasia, liver disease, mental disorders, and thyroid disorders) were excluded.

Meticulous medical history and full general and dermatological examination were performed. Acne severity was evaluated in patients group using Global Acne grading System (GAGS).[9] Body mass index (BMI) was calculated for each participant. A BMI of 25.0 to 29.0 kg/m^2 was considered overweight, while a BMI of 30 kg/m^2 or greater was considered obese. BMI was calculated using the weight (kg)/height (m) formula (m^2).[10]

3 | TREATMENT PLAN, LABORATORY INVESTIGATIONS AND ULTRASONOGRAPHY

All patients received low-dose isotretinoin (0.25–0.4 mg/kg/day mean 0.29 ± 0.053) for 6 months. In patient group, assessment of serum AMH, ultrasonographic (US) assessment of ovarian volume (OV) and antral follicle count (AFC) were performed before starting isotretinoin treatment and 6 months after the last dose. In control subjects, assessment of serum AMH, OV and AFC were performed at baseline date then 1 year thereafter. AFC was defined as the number of follicles measuring 2–10 mm in diameter as assessed by US.

Enzyme-linked immunosorbent assay (ELISA) using Human Mullerian Inhibiting Substance/Anti-Mullerian hormone ELISA commercial kits (Catalogue No. 201–12-1053) was used to measure serum level of AMH on the 2nd–5th day of the menstrual cycle. Suprapubic pelvic ultrasonography (Mindray DC-70, Mindray Medical Systems, China, 3.5 to 5 mHz, convex probe) was performed in the same time period by an experienced gynecologist to calculate the OV and AFC.

4 | STATISTICAL ANALYSIS

SPSS 26.0 for Windows was used to gather, tabulate, and statistically analyze all the data (SPSS Inc., Chicago, IL, USA). The mean ± *SD* was used to express quantitative data. The Student's *t*-test was used to compare two groups of normally distributed variables, and the paired *t* test was employed to compare pre- and post-treatment findings in each group.

To analyze the relations between different variables studied, the Pearson correlation coefficient was determined. The (+) sign indicates direct correlation, while the (−) sign indicates inverse correlation. Values around 1 suggest strong correlation, while values near 0 indicate weak correlation.

All the tests were two- sided. A *p*-value of less than 0.05 was regarded statistically significant, while a *p*-value of more than 0.05 was judged statistically non-significant.

5 | RESULTS

Patients and control subjects were age- matched (mean age 28.28 ± 4.5 years vs. 28.17 ± 4.2 years respectively) ($p = 0.874$). There was also insignificant difference in BMI between both groups (25.84 ± 3.7 and 25.95 ± 3.7 in patients and control groups respectively) ($p = 0.857$).

Patients with moderate ($n = 41$) and severe ($n = 25$) acne (GAGS mean 29.53 ± 4.7) were treated with low dose Isotretinoin for 6 months.

There was no significant difference in baseline level of AMH between patients and control subjects ($p = 0.920$). Similarly, AMH levels did not show any significant difference when compared 6 months after the last isotretinoin dose in patients' group and 1 year after the baseline assessment in the control subjects ($p = 0.898$). At the level of each group, AMH failed to show any significant change in pre- and post- treatment levels in patients' group, and in baseline and after a one-year-interval levels in control group ($p = 0.747$ and 0.361 respectively).

The baseline ovarian volume (OV) was insignificantly different in patients and control subjects on both left ($p = 0.099$) and right ($p = 0.138$) ovaries. This insignificant change was also evident after isotretinoin treatment in patients and 1 year after baseline assessment

TABLE 1 Mean levels and mean changes in anti-Müllarian hormone (AMH), ovarian volume (OV) and antral follicle count (AFC) in patient group before and after isotretinoin therapy, and in control subjects as baseline level and 1 year thereafter

Variable		Patient group ($N = 66$) (Mean ± *SD*)	Variable	Control group ($N = 66$) (Mean ± *SD*)	Test *t*	Test *p* value
AMH (ng/ml) before treatment		3.35 ± 0.77	AMH-baseline	3.36 ± 0.83	−0.1	0.920
AMH (ng/ml) after treatment		3.34 ± 0.77	AMH- 1 year after	3.37 ± 0.83	−0.129	0.898
Paired *t* test	*Test*	−0.324		−0.920	–	
	p value	0.747		0.361		
OV (ml^3) Rt before treatment		8.94 ± 1.11	OV Rt - baseline	8.64 ± 1.19	1.491	0.138
OV Rt after treatment		8.94 ± 1.11	OV Rt- 1 year after	8.59 ± 1.22	1.688	0.094
Paired *t* test	*t*	−0.293		1.893	–	
	p value	0.771		0.063		
OV Lt before treatment		8.17 ± 1.07	OV Left–baseline	7.85 ± 1.11	1.663	0.099
OV Lt after treatment		8.17 ± 1.08	OV Left- 1 year after	7.86 ± 1.12	1.610	0.110
Paired *t* test	*t*	0.292		−0.191	–	
	p value	0.771		0.849		
AFC Rt before treatment		10.79 ± 2.18	AFC Right- baseline	11.42 ± 2.38	−1.602	0.112
AFC Rt after treatment		10.77 ± 2.25	AFC Right- 1 year after	11.33 ± 2.15	−1.460	0.147
Paired *t* test	*t*	0.136		0.736	–	
	p value	0.892		0.464		
AFC Lt before treatment		9.79 ± 2.18	AFC Left- baseline	10.42 ± 2.38	−1.602	0.112
AFC Lt after treatment		9.93 ± 1.84	AFC Left- 1 year after	10.3 ± 2.18	−1.037	0.302
Paired *t* test	*t*	−1.010		1.016	–	
	p value	0.316		0.313		

Note: A *p*-value < 0.05 was regarded statistically significant.
Abbreviations: SD, standard deviation; *t*, Student *t*-test.

in control group on both sides ($p = 0.110$ and 0.094 on left and right sides respectively).

The AFC also showed insignificant difference between patients and control subjects both at baseline and 1 year thereafter on both left and right ovaries ($p = 0.112$, 0.302, 0.112, and 0.147 respectively).

Both OV and AFC showed no significant changes in patient group when comparing pre- post- treatment levels on both sides ($p > 0.05$) and in control group when baseline and 1-year-interval levels were compared on both sides ($p > 0.05$) (Table 1) (Figure 1).

Besides, baseline AMH and AFC were found to have significant negative correlation with BMI and severity of acne (GAGS) in studied patients. Also, significant negative correlation was found between OV and BMI. While the changes in the studied parameters remain unrelated to age, OV appears to be the only variable that correlates positively with age in our studied patients (Table 2).

6 | DISCUSSION

Being the only medication that affects all etiopathological aspects of acne, systemic isotretinoin is rapidly gaining popularity as the "most effective" acne treatment. Nevertheless, plenty of side effects has been reported since its very early use. Studies continue to emerge addressing the effect of oral isotretinoin on female fertility.[11–16] Googling: "Does isotretinoin affect future pregnancy?" revealed more than 200.000 results addressing those concerns about the effect of the medication on future fertility might be an issue.

The aim of this work was to evaluate the effect of low dose isotretinoin (0.25–0.4 mg/kg/day mean 0.29 ± 0.053) used in treatment of moderate to severe acne (mean GAGS 29.53 ± 4.7) for 6 months on OR.

Isotretinoin dosage used to be estimated based on body weight, usually 0.5–1 mg/kg per day, and recommended for long enough to reach a cumulative dose of about 150 mg/kg.[17] This appears to be lacking evidence. The general trend of using low dose isotretinoin, regardless the body weight, is rapidly growing and gaining evidence.[18]

Our results showed insignificant change in serum AMH level in terms of pre- and post- treatment assessment levels ($p = 0.747$). of note, there was also insignificant difference when baseline AMH levels were compared with the control subjects ($p = 0.920$). Similar insignificant changes were noted in OV and AFC ($p > 0.05$). AMH, a transforming growth factor β (TGF β) family member, is currently considered an easy-to assess sensitive serum marker of OR and hence ovarian functions.[19] AFC is an estimation of the number of ovarian follicles, also described as OR.[5] In comparison to follicle stimulating

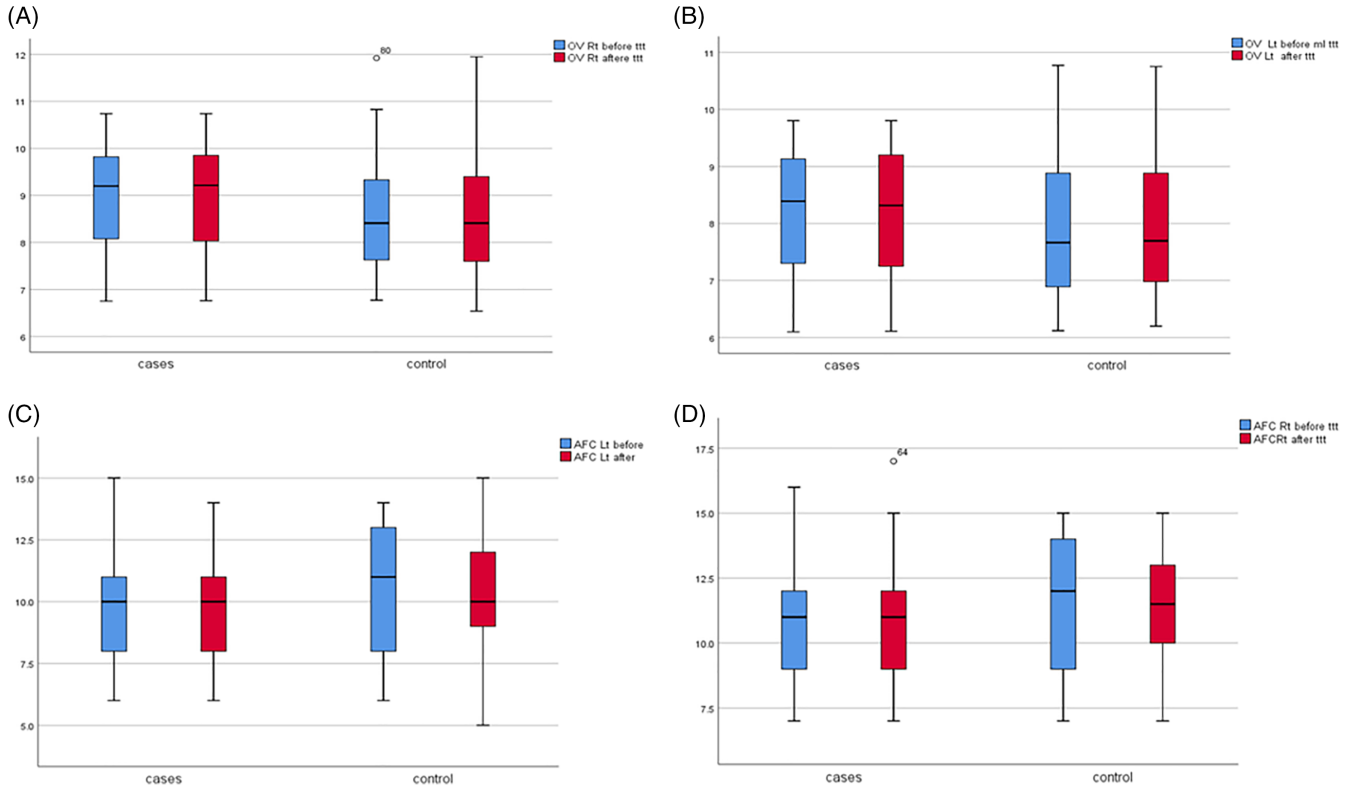

FIGURE 1 Box plot graphs: (A): Main change in ovarian volume (OV) in right ovary among studied groups. (B): Main change in OV in left ovaries among studied groups. (C): Main change in antral follicle count (AFC) in right ovary among studied groups. (D): Main change in AFC in left ovary among studied groups

TABLE 2 Correlation between age (years), BMI (Kg/m^2), GAGS and anti-Mullarian hormone (AMH), ovarian volume (OV) and Antral follicle count (AFC) within studied groups

Variables		Age (years)	BMI[a] (kg/m^2)	GAGS[b]
AMH before treatment (ng/ml)	*r*	0.070	−0.647[c]	−0.577[c]
	p	0.578	0.000	0.000
AMH after treatment	*r*	0.056	−0.653[c]	−0.583[c]
	p	0.657	0.000	0.000
OV (Right) before treatment	*r*	0.738[c]	−0.256*	0.011
	p	0.000	0.038	0.930
OV (Right) After treatment	*r*	0.747[c]	−0.246*	0.027
	p	0.000	0.046	0.828
OV (Left) before ml treatment	*r*	0.810[c]	−0.328[c]	−0.026
	p	0.000	0.007	0.835
OV (Left) after treatment	*r*	0.805[c]	−0.328[c]	−0.026
	p	0.000	0.007	0.836
AFC (Right) before treatment	*r*	0.068	−0.533[c]	−0.554[c]
	p	0.588	0.000	0.000
AFC (Right) after treatment	*r*	−0.021	−0.552[c]	−0.605[c]
	p	0.866	0.000	0.000
AFC (Left) before treatment	*r*	0.068	−0.533[c]	−0.554[c]
	p	0.588	0.000	0.000
AFC (Left) after treatment	*r*	−0.023	−0.434[c]	−0.488[c]
	p	0.854	0.000	0.000

Abbreviation: r, Spearman coefficient.
[a]Body mass index.
[b]Global acne grading scale.
[c]Statistically significant at $p < 0.05$.
*$p < 0.05$ statistical significance.

hormone (FSH), estradiol (E2), inhibin B levels, and several ovarian challenge tests, AMH proves to have the highest sensitivity and specificity in evaluating ovarian functions.[20]

Results of previous studies were controversial. Multiple studies reported significant decrease in AMH level after isotretinoin therapy.[11,13,14] Of note, these results were reported after a total cumulative dose of 120–150 mg/kg. Korkomaz et al. noted significant reduction in AMH levels immediately after isotretinoin therapy in Sprague–Dawley albinos, but this was reversed after 1 month of treatment cessation.[12] In the same context, Cinar et al. reported that the significant decrease in AMH level following isotretinoin therapy was totally reversible after 18 months following the last isotretinoin dose.[11] Can et al. compared the effect of high and low dose isotretinoin on AMH levels. They reported a more significant decrease in AMH level following high dose treatment when compared to low dose treatment group.[8] These results along with ours suggest that the toxic effect of isotretinoin on the granulosa cells (AMH- secreting cells) may be dose dependent.

An essential step in the mechanism of action of isotretinoin is its isomerization to all-trans-retinoic acid that, in turn, induces apoptosis via upregulation of *FoxO1* gene expression mainly in sebocytes producing the main therapeutic effect, and in other population of cells -including granulosa cells- producing various adverse effects.[21,22] Whether this effect on granulosa cells is dose dependent or not should be an upcoming target of research.

We found no significant changes in OV and AFC in terms of pre- and post-treatment evaluation and when compared to control group. This is in opposition to Öztürk et al. who reported significant decrease in both following isotretinoin therapy.[16] Once again, this controverse may be due to different dosage regimens. Other researchers confirmed that this significant decrease was temporary as well.[11,12]

A significant negative correlation was found between AMH levels and AFC on one hand and BMI on the other hand. Reproductive functions in females have long been linked to obesity.[23] It is now well established that metabolism of hormones is affected in adipose tissue. In addition, obesity can exert an apoptotic effect on granulosa cells and may affect the levels of AMH even in non- polycystic ovary (PCO) patients.[24]

Exclusive enrolment of non- PCO patients, the relatively short follow-up period and the relatively small sample size are limitations to our study.

7 | CONCLUSION

Low- dose isotretinoin in treatment of moderate to severe acne seems to be safer on ovarian reserve than the full- dose regimen as indicated by non-significant change in AMH levels as a sensitive parameter of female fertility.

AUTHOR CONTRIBUTIONS

Asmaa M. Haroun: collected the data and performed the analysis. Menha A. Ibrahim: designed the study and overall supervision. Ahmed S. Soliman: performed the gynecological examination and sonography/ paper writing. Amira O. Abdel-Ghaffar: performed the lab work and contribute to data analysis and paper writing. Ghada M. Shams: designed the study/ treatment and dermatological examination /data collection and analysis/ paper writing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The work has been approved by the Scientific Ethics Committee of Faculty of Medicine (MS: 31-7-2019), according to Helsinki Declaration principles. Written informed consent was filled by subjects before being included in this study.

ORCID

Ahmed S. Soliman https://orcid.org/0000-0001-7856-6440
Ghada M. Shams https://orcid.org/0000-0002-9781-9244

REFERENCES

1. On SCJ, Zeichner J. Isotretinoin updates. *Dermatol Ther*. 2013;26(5):377-389. doi:10.1111/dth.12084
2. Rosa FW. Teratogenicity of isotretinoin. *Lancet*. 1983;2:513. doi:10.1016/S0140-6736(83)90538-X
3. Schaefer C, Meister R, Weber-Schoendorfer C. Isotretinoin exposure and pregnancy outcome: an observational study of the Berlin institute for clinical teratology and drug risk assessment in pregnancy. *Arch Gynecol Obstet*. 2009;281(2):221-227. doi:10.1007/s00404-009-1112-2
4. Melnik B. Apoptosis may explain the pharmacological mode of action and adverse effects of isotretinoin, including teratogenicity. *Acta Derm Venereol*. 2017;97(2):173-181. doi:10.2340/00015555-2535
5. Gruijters MJ, Visser JA, Durlinger AL, Themmen AP. Anti-Müllerian hormone and its role in ovarian function. *Mol Cell Endocrinol*. 2003;211(1–2):85-90. doi:10.1016/j.mce.2003.09.024
6. Kunt C, Ozaksit G, Keskin Kurt R, et al. Anti-Mullerian hormone is a better marker than inhibin B, follicle stimulating hormone, estradiol or antral follicle count in predicting the outcome of in vitro fertilization. *Arch Gynecol Obstet*. 2011;283(6):1415-1421. doi:10.1007/s00404-011-1889-7
7. Alkhaldy HY, Assiri AM, Fatima S, Owaidah T. Isotretinoin is active in the initial management of acute pro-myelocytic leukemia. *Leuk Res Rep*. 2020;14:100220. doi:10.1016/j.lrr.2020.100220
8. Can P, Kocatürk E, Mihmanlı V, Sucu V, Degirmentepe E, Kızıltaç U. The evaluation of ovarian reserve and menstrual irregularities in female patients treated with systemic isotretinoin. *TURKDERM*. 2020;54:79-84. doi:10.4274/turkderm.galenos.2020.37974
9. Doshi A, Zaheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. *Int J Dermato*. 1997;36(6):416-418.
10. Centers for Disease Control and Prevention, Division of Nutrition, Physical Activity and Obesity, National Center for Chronic Disease Prevention and Health Promotion. (2011). Body Mass Index. Accessed August, 31, 2022 from http://www.cdc.gov/healthyweight/assessing/bmi/index.html.
11. Cinar SL, Kartal D, Aksoy H, et al. Long-term effect of systemic isotretinoin on female fertility. *Cutan Ocul Toxicol*. 2016;36(2):132-134. doi:10.3109/15569527.2016.1172234

12. Korkmaz E, Cetinkaya N, Oz M, et al. The possibly reversible isotretinoin effect of decreased ovarian reserve in sprague-dawley albinos: part I, biochemical analyses. *Gynecol Obstet Invest*. 2016;82(1):72-77. doi:10.1159/000445294
13. Aksoy H, Cinar L, Acmaz G, et al. The effect of isotretinoin on ovarian reserve based on hormonal parameters, ovarian volume, and antral follicle count in women with acne. *Gynecol Obstet Invest*. 2015;79(2):78-82. doi:10.1159/000371551
14. Şikar Aktürk A, Abalı R, Yüksel MA, Güzel EE, Güzel S, Kıran R. The effects of isotretinoin on the ovarian reserve of females with acne. *Gynecol Endocrinol*. 2013;30(1):30-33. doi:10.3109/09513590.2013.860118
15. Abali, R., Yuksel, M. A., Aktas, C., Celik, C., Guzel, S., Erfan, G., & Sahin, O. (2013). Decreased ovarian reserve in female Sprague–Dawley rats induced by isotretinoin (retinoic acid) exposure. *Reprod Biomed Online*, 27(2), 184–191. 10.1016/j.rbmo.2013.04.010
16. Öztürk S, Öztürk T, Ucak H, et al. Evaluation of ovarian reserve and function in female patients treated with oral isotretinoin for severe acne: an exploratory study. *Cutan Ocul Toxicol*. 2014;34(1):21-24. doi:10.3109/15569527.2014.888079
17. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol*. 2016;74(5):945-73.e33. doi:10.1016/j.jaad.2015.12.037
18. Oakley A. Isotretinoin. DermNet NZ; 2016. Available from: http://dermnetnz.org/treatments/isotretinoin.html (Accessed June, 2022).
19. Moolhuijsen LME, Visser JA. Anti-Müllerian hormone and ovarian reserve: update on assessing ovarian function. *J Clin Endocrinol Metabol*. 2020;105(11):3361-3373. doi:10.1210/clinem/dgaa513
20. Iwase A, Nakamura T, Osuka S, Takikawa S, Goto M, Kikkawa F. Anti-Müllerian hormone as a marker of ovarian reserve: what have we learned, and what should we know? *Reprod Med Biol*. 2015;15(3):127-136. doi:10.1007/s12522-015-0227-3
21. Melnik B. Isotretinoin and FoxO1. *Derma Endocrinol*. 2011;3(3):141-165. doi:10.4161/derm.15331
22. Shen M, Lin F, Zhang J, Tang Y, Chen WK, Liu H. Involvement of the up-regulated FoxO1 expression in follicular granulosa cell apoptosis induced by oxidative stress. *J Biol Chem*. 2012;287(31):25727-25740. doi:10.1074/jbc.m112.349902
23. Moslehi N, Shab-Bidar S, Ramezani Tehrani F, Mirmiran P, Azizi F. Is ovarian reserve associated with body mass index and obesity in reproductive aged women? *A Meta-Analysis Menopause*. 2018;25(9):1046-1055. doi:10.1097/gme.0000000000001116
24. Jungheim ES, Travieso JL, Hopeman MM. Weighing the impact of obesity on female reproductive function and fertility. *Nutr Rev*. 2013;71:S3-S8. doi:10.1111/nure.12056

How to cite this article: Haroun AM, Ibrahim MA, Soliman AS, Abdel-Ghaffar AO, Shams GM. Systemic isotretinoin for acne treatment: Ovarian reserve is safe with the low dose. *Dermatologic Therapy*. 2022;35(11):e15811. doi:10.1111/dth.15811