

1 **Source:** [The effect of luteal phase gonadotropin-releasing hormone antagonist administration on](#)
 2 [IVF outcomes in women at risk of OHSS](#), by Maryam Eftekhar, Sepideh Miraj, and Zahrasadat
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4 **The Effect of luteal phase gonadotropin-releasing hormone antagonist administration on in**
 5 **vitro fertilization IVF outcomes in women at risk of ovarian hyperstimulation syndrome: A**
 6 **retrospective study OHSS**

7
 8 **Short title:** Luteal phase GnRH antagonist effects on IVF outcomes in women with OHSS risk

9 **Authors:**

10 **Affiliations:**

11
 12 ***Corresponding Author:**

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14

Commented [A1]: Dear Author,
 Thank you for this opportunity to assist you on your manuscript. I have checked the manuscript for language, grammar, readability, consistency, and flow, and formatting per the target journal guidelines (<https://journals.plos.org/plosone/s/submitting-guidelines>). Please let me know in case you have further queries or doubts regarding the revisions. Do go through my comments in the manuscript and in the attached letter for more detail on my work and the changes I have made.

All my best wishes!!

Commented [2]: The title may be up to 250 characters. Your current title is well within this limit. I have added the study design to the title in line with journal preferences

Please use this title at all instances going forward.

Commented [3]: In general, avoid using abbreviations in manuscript titles. PLOS One recommends submitting authors to avoid specialist abbreviations if possible. Therefore, I have spelled out the abbreviations used in this title to adhere to this instruction.

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Author names will be published exactly as they appear in the accepted manuscript. Indicate affiliations by number only. Affiliation footnotes should appear in numerical order at first mention. Please use the symbols provided in this document for other designations. Numbers and symbols should be in superscript.

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Abstract

Background: Gonadotropin-releasing hormone (GnRH) plays an essential role in embryo implantation, invasion of trophoblastic tissue, and steroid synthesis in the placenta. However, evidence on the effects of gonadotropin-releasing hormone antagonists on pregnancy outcomes is limited.

Objective: The aim of this study was to evaluate the effect of GnRH-gonadotropin-releasing hormone GnRH antagonist administration during the early implantation period on pregnancy outcomes in early implantation period.

Materials and Methods: In this retrospective study included 94 infertile women at risk of ovarian hyperstimulation syndrome undergoing gonadotropin-releasing hormone GnRH antagonist protocol who were at risk of ovarian hyperstimulation syndrome (OHSS) were included. Sixty-seven patients (group I) received Cetorelix 0.25 mg/daily in the luteal phase during the luteal phase for 3 days, while in 27 participant patients (group II) did not receive it, it was not administered. Pregnancy outcomes were assessed based on chemical and clinical pregnancy rates.

Results: The pregnancy outcomes were not significantly different between the two groups ($p=0.224$).

Conclusion: This present study proposed that luteal phase gonadotropin-releasing hormone GnRH antagonist administration during the luteal phase does not affect influence the chance probability of successful pregnancy outcomes.

Key Words: Gonadotropin-releasing hormone antagonist, Pregnancy outcome, In vitro fertilization

Introduction

Commented [8]: The headings have been reformatted per the following journal guideline: Use Level 1 heading for all major sections (Abstract, Introduction, Materials and methods, Results, Discussion, etc.). • Bold type, 18 pt font. • Only use italics and text formatting where needed (e.g. genus and species names, genes, etc.). • Headings should be written in sentence case (capitalize only the first word of the heading, the first word of the subheading, and any proper nouns and genus names).

Commented [9]: Please note that the abstract, per the guidelines should be less than 300 words, and should not include abbreviations, if possible. The word count is well within 300 words.

Accordingly, I have removed the abbreviations from the abstract.

Since there is no specific guideline regarding the structure of the abstract, I have retained your original style.

Commented [A10]: I have added a sentence describing the gap in the current literature with respect to the topic of study. Please consider adding a statement that provides some background information on GnRH antagonists.

Commented [11]: Consider adding a sentence on the statistical tests used to analyze data.

Commented [12]: Please consider providing more details regarding the critical results of the study. This might be considered a little too abrupt and readers may not want to read the entire study if they get the impression that this was the only point worth noting. Patient mean age and implantation rates can be mentioned, for example.

Commented [A13]: Chemical and clinical pregnancies are different concepts; thus, ideally two p values should be provided to indicate that there was no significant difference.

Commented [A14]: The conclusion of the abstract should refer only to the tested Cetorelix, and not to GnRH antagonists in general. There are several GnRH antagonists such as Elagolix, Degarelix, but these have not been studied here.

Commented [A15]: Please considering discussing the implications and applications of these findings in the clinical field at large.

Commented [16]: There is no specific guideline regarding the key words. Please verify with the journal whether these are required and remove them if not required.

39 Female genital ~~tissues-organs like such as~~ the ovaries, endometrium, and placenta are ~~extra-extra-~~
 40 pituitary tissues ~~which that~~ express Gonadotropin-releasing hormone (GnRH) receptors ~~([1])~~. GnRH
 41 plays essential roles in embryo implantation, invasion of trophoblastic tissue, and steroid synthesis in
 42 the placenta ~~([2])~~. ~~There are limited evidences-evidence is available regarding of the effects of~~
 43 GnRH antagonists' effects on pregnancy outcomes.
 44 Several protocols such as GnRH antagonist protocol ~~were have been~~ used for in vitro fertilization
 45 (IVF) ~~([3, 4])~~. Previous studies ~~have~~ evaluated the role of GnRH antagonists in women with poor
 46 response to ovulation stimulation. Some studies ~~have were~~ demonstrated GnRH antagonists ~~is to be~~
 47 comparable ~~withto~~ GnRH agonists ~~([5, 6])~~. The most important GnRH antagonist benefits ~~are~~
 48 ~~includinginclude:- decrease the reduced need-ofrequirement for~~ exogenous gonadotropin, shorter time
 49 for stimulation, and a ~~cost-effective~~ protocol ~~([3, 4, 7-9])~~.
 50 ~~Also-Further~~, GnRH antagonists causes ~~the~~-regression of established severe ovarian hyper-stimulation
 51 syndrome (OHSS) by luteolysis as ~~a-the~~ key mechanism in ~~the~~ prevention of OHSS ~~([2])~~. ~~After-The~~
 52 ~~introductioni-~~ of GnRH antagonists ~~into-in~~ clinical practice ~~led to,-it~~ reduced OHSS rates in
 53 IVF/~~intracytoplasmic sperm injection (ICSI)~~ cycles ~~([9])~~. GnRH antagonists can ~~alleviateimprove the~~
 54 poor responses to ovulation stimulation ~~([6, 10, 11])~~. ~~Although-Many~~ ~~mstudies~~ ~~showed-have~~
 55 ~~reported~~ the benefits of GnRH antagonists on IVF/ICSI cycle outcomes; ~~however,-but-their~~ ~~its~~ effect
 56 ~~is-remains~~ controversial. The use of GnRH antagonists is generally limited to the last few days of
 57 ovulation in IVF/ICSI cycles.

58 The aim of this study was to evaluate the ~~effects of~~ GnRH antagonist ~~administration effects-at~~
 59 pharmacological doses ~~given-in-during the~~ early implantation period on pregnancy outcomes.

60 Materials and Methods

61 In this retrospective study, medical records of 94 women ~~that-who~~ were at risk of OHSS in IVF/ICSI
 62 cycles and ~~has-been-were~~ referred to the Research and Clinical Center for Infertility, Yazd, Iran,
 63 between October 2014 and February 2015 were reviewed. ~~The~~ study protocol was approved by the

Commented [L17]: In academic writing, ideas need to be conveyed using formal language. I have revised this term to a better academic term alternative.

Commented [L18]: In American English, the pronoun 'which' is usually used to introduce nonessential information, and the pronoun 'that' is used to include essential information. For example, 'The windows, which have red crosses, are sealed' implies that the windows are sealed, and they incidentally have red crosses. However, 'The windows that have red crosses are sealed' implies that only the windows with red crosses are sealed.

Commented [L19]: Intext citations have been reformatted per the preferred journal style.

Commented [A20]: Please consider adding a sentence or two providing background information on GnRH antagonists before talking about the limited evidence on their effects on pregnancy.

Commented [L21]: Avoid beginning sentences and clauses with the overly general "There is," "There are," or "There were" in academic writing. These are just empty filler words.

Commented [A22]: A new paragraph has been started here for better flow.

Commented [L23]: Were these comparable in terms of their effects? Please provide the missing information.

Commented [L24]: It may be a good idea to explain this term and its application briefly for the benefit of the readers.

Commented [A25]: While comparing GnRH agonists and antagonists in the Introduction, it would be good to include a comprehensive reference, such as a meta-analysis: <https://pubmed.ncbi.nlm.nih.gov/28903472/>; <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0109133>; <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0106854>

Commented [L26]: A compound adjective is formed by two words that jointly describe a noun (e.g., 'water' and 'soluble' in 'water-soluble compound'). Such compound adjectives are usually hyphenated to indicate that they form a single unit. The use of the hyphen also aids clarity. For example, in the sentence 'I saw a man-eating alligator,' it is clear that t... [1]

Commented [L27]: I suggest moving this part of the text to after the second reference citation in the previous paragraph for better flow. Please let me know if you agree with this change, and we can do it for you. ... [2]

Commented [L28]: In academic writing, it is customary to provide an expansion of the abbreviation when first used. I have provided the expansion here.

Commented [A29]: The research rationale needs to be better formulated. In lines 45-48, you report the benefits of GnRH antagonists on IVF/ICSI cycles outcomes. You then state that the effects remain controversial. Where doe... [3]

Commented [A30]: Please clearly state the novelty of the study. Have no previous studies studied the effects of GnRH antagonist administration during the early implantation period on pregnancy outcomes.

64 ethics committee of the Research and Clinical Center for Infertility, Yazd, Iran, and oral consent was
 65 obtained from all ~~partieipantpatients~~.

66 Inclusion criteria were ~~women age <under 40 years old~~, having more than 20 follicles (>14 mm) at
 67 triggering time, and ~~en-being at~~ risk of OHSS during the ~~ICSI-IVF/ICSI~~ cycle with embryo transfer.

68 Women with a history of endometriosis, ~~history-of or~~ more than ~~2two~~ implantation failures, and those
 69 with severe male factor ~~infertility~~ were excluded.

70 ~~Totally~~Overall, 94 eligible women were studied in two groups. All ~~partieipantpatients~~ were treated
 71 with the GnRH antagonist protocol. Patients received recombinant human follicle-stimulating
 72 hormone (Gonal-F) (150 IU, subcutaneously) for 5 days. Serial transvaginal-vaginal sonography was
 73 performed. When the a mature follicle (≥ 14 mm) was detected, GnRH antagonist (~~Cetrorelix~~
 74 (~~Cetrotide~~) (0.25 mg/daily, ~~subcutaneously~~) was injected ~~subcutaneously~~. Triggering was started
 75 initiated with 1500 IU hCG (Pregnyl, Organon, Netherland) and 0.2 mg GnRH-a (Decapeptyl[®], 0.1
 76 mg) (~~subcutaneously~~) injection when at least two follicles with a mean diameter of 17 mm ~~was were~~
 77 observed.

78 ~~Trans-vaginal~~Transvaginal egg retrieval was performed ~~egg retrieval was done~~ under sedation after
 79 36 ~~hrs~~hours. ~~Sixty-seven~~67 women received 25 mg ~~Cetrorelix~~Cetrotide subcutaneously for 3 days
 80 from the day of oocyte retrieval (case group) and 27 ~~partieipantpatients~~ did not receive
 81 ~~Cetrorelix~~Cetrotide in luteal phase ~~during the luteal phase~~ (control group). ~~2Two~~ embryos were
 82 transferred 48 hours after oocyte retrieval using an embryo transfer Labotect catheter (Labotect
 83 ~~Gmbh~~-Labor-Technik-Göttingen GmbH, ~~Göttingen~~Göttingen, Germany) ~~In in~~ all patients. All
 84 transferred embryos were in grade A and B. Progesterone suppositories (Cyclogest[®]) 400 mg twice
 85 in a day, ~~was were~~ used vaginally on the day of oocyte collection for luteal phase support; ~~and it~~
 86 ~~continued~~ until the fetal heart activity was documented ~~viaby~~ ultrasonography. Serum beta-hCG (β -
 87 hCG) ~~levels wasere~~ assessed on day 14 after embryo transfer.

88 ~~PA positive~~ pregnancy test was ~~define~~ defined as β -hCG levels >50 IU/L. Pregnancy outcomes were
 89 assessed based on clinical pregnancy ~~rates~~ (observation of fetal heart activity ~~onby~~ transvaginal

Commented [31]: Please mention the approval number here, if available.
 As per the guidelines, All research involving human patients must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s), and must have been conducted according to the principles expressed in the [Declaration of Helsinki](#). You may mention this specifically.

Commented [32]: Please verify if this was only oral, or written consent was also taken.

Further, per the guidelines, Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

Commented [33]: When expressing numbers (both cardinal and ordinal) within your text, write numbers one through nine alphabetically and write numbers 10 and above numerically, except when the numerals indicate time periods or are followed by units of measurement.

Commented [34]: For academic writing, the product name, model number, **manufacturer, and country** should be mentioned within the parenthesis. Please provide the missing information.

Commented [35]: The missing information should be inserted here as well.

Commented [36]: Does this apply for both hCG and GnRH-a? I have assumed this and removed the parentheses. If only applicable for GnRH-a, this can be added within the previous set of parentheses as (Decapeptyl, 0.1 mg, subcutaneous administration)

Commented [37]: Starting a sentence, title, or heading with a numeral is considered slightly informal in academic writing and should be avoided. You could either reconstruct the sentence such that you do not have to start the sentence with a number or you could spell out the numeral. Avoid: "20 college students participated in this study." Better: "Twenty college students participated in this study" OR "The participants were 20 college students."

90 ultrasonography 2-3 weeks after positive β -hCG). Implantation rate was defined as the ratio of the
91 number of gestational sacs to the number of embryos transferred.

92 **Statistical analysis**

93 All of statistical analyses were done performed by using SPSS 20 (SPSS, Chicago, IL). The
94 normal distribution of data was checked. Mean \pm SD values were calculated for descriptive analysis.
95 The independent t-test and χ^2 test were used. The level of statistical significances considered as was
96 set at 0.05. According with to the power analysis, the power of the study was 0.8 and α was 0.05.

97 **Results**

98 The mean age of participant patients was 28.56 \pm 4.03 years in the case group and 28.03 \pm 4.8 years in
99 the control group. Basic characteristics of participant patients in the groups are shown summarized in
100 Table 1-table I. There were not No statistical significant ly differences were noted in age, duration of
101 infertility, and basal serum follicle-stimulating hormone FSH serum, progesterone, and estradiol
102 levels in on the day of HCG triggering between the groups. While However, the mean number of
103 embryos was different between the groups (Table 1)-(Table I). The pregnancy outcome was not
104 significantly different between case and control group (p=0.224). The implantation rate was 14.39%
105 in case group and 9.25% in controls (p=0.089) (Table II).

107 **I**

108 **The basic Data are presented as mean \pm SD. *Independent Students' Test in s II Table 1: I**

109 **Baseline characteristics of patients in the two groups**

Commented [38]: Are you referring to confirmation of a positive pregnancy or β -hCG levels >50 IU/L? If so, I recommend phrasing in either of these ways for clarity. Else, "test results" can be added after "positive β -hCG."

Commented [39]: Please note that I made this formatting change to clearly identify different levels of headings.

Level 2 Heading • Use Level 2 headings for sub-sections of major sections. • Bold type, 16 pt font. • Only use italics and text formatting where needed. • Use sentence case.

Commented [A40]: While discussing the power analysis, you should also mention the adequacy of the sample size, stemming from the analysis itself.

Commented [41]: Commas are typically used to separate elements in a series (e.g., "I've visited Japan, the UK, and Egypt"), but semicolons are used if the elements themselves contain commas (e.g., "I've visited Japan, Thailand, and China in Asia; the UK, Belgium, and France in Europe; and Egypt, Morocco, and Kenya in Africa").

Commented [42]: Was this significantly different? If so, please mention the p-value.

Commented [43]: As per the guidelines, the tables are inserted immediately after the first paragraph in which they are cited. Hence, I have moved them from the end of the manuscript to within the manuscript close to where they are first cited.

Commented [44]: I made this change per the preferred journal style.

Variables	Case group (n=67)	Control group (n=27)	p-value *
Age (years)	28.56 ± 4.03	28.03 ± 4.8	0.593
3 rd day 3 FSH level	5.76 ± 2.73	5.71 ± 3.42	0.942
Infertility duration (years)	6.73 ± 3.85	6.66 ± 4.49	0.942
Serum progesterone** (ng/ml)	1.09 ± 0.55	1.11 ± 0.55	0.924
Serum estradiol** (pg/mL)	3337.07 ± 514.44	3301.63 ± 459.04	0.756

Commented [A45]: The journal guidelines do not mention anything about the use of abbreviations in tables. Please confirm with the journal whether abbreviations used only once should outright avoided in the tables or whether abbreviations should be defined below each respective table.

Commented [L46]: Please mention the measuring unit for this metric.

110 Data are presented as mean±SD.

111 *Independent Students's t-test.

112 ** on the day of HCG triggering

113

114 The pregnancy outcome was not significantly different between the groups (p=0.224). The

115 implantation rate was 14.39% in the case group and 9.25% in the control group (p=0.089) (Table 2).

116

117

118

119 **Table 2H**

Commented [L47]: Use "in" to refer to a general, longer period of time, such as months, years, decades, or centuries. For example, we say "in April," "in 2015" or "in the 21st century." When referring to shorter, more specific periods of time, use "on" to talk about particular days, dates, and holidays, for example, "I went to work on Monday" or "Let's have a picnic on Memorial Day." For the most specific times, use "at," for example, "Meet me at midnight," or "The flowers are in bloom at Easter time."

120 **ART outcomes in the two studied study groups**

	Case group (n=67)	Control group (n=27)	p-value *
Number of oocytes ^a	19.86 ± 4.94	18.51 ± 2.84	0.023
Number of embryos ^a	6.31 ± 5.21	5.22 ± 4.06	0.332
Clinical pregnancy rate ^b	19 (28.78%)	5 (18.51%)	0.224
Implantation rate	14.39%	9.25%	0.089

121 ^aData are presented as mean±SD.122 ^bData are presented as n(%).

123

124 * χ^2 test

125

126

127

128 **Discussion**

Commented [L48]: Please provide the expanded form for this abbreviation after confirming the guidelines on abbreviation use in tables.

129 Our results ~~showed~~ ~~indicated~~ that ~~luteal phase~~ GnRH antagonist ~~administration during the luteal phase~~
 130 ~~administration~~ did not ~~influence~~ ~~affect~~ the ~~chance~~ ~~probability~~ of pregnancy. The clinical pregnancy rate
 131 ~~in studied groups~~ was not significantly different ~~between the study groups~~. Triggering of final oocyte
 132 maturation by hCG induces massive luteinization, increase ~~in the secretion of~~ angiogenic factors
 133 ~~secretion~~ (such as angiotensin II, interleukins, vascular endothelial growth factor, histamine, prolactin,
 134 prostaglandins, endothelin-1, and selectins) from ~~the corpus luteums~~ ~~luteum~~ of hyperstimulated
 135 ovaries. ~~It leads to~~ development of OHSS ~~by due to~~ increase in vascular permeability, and finally,
 136 fluid shift to the third space ([12-15]).

137 Previous studies ~~have~~ reported that GnRH antagonist administration ~~in the luteal phase~~ ~~during the~~
 138 ~~luteal phase~~ ~~improved~~ severe OHSS ~~within two~~ ~~2~~ days ~~after of the~~ injection of GnRH antagonist by
 139 decreasing the ovarian volume, hematocrit, ascites, and ~~oestradiol~~ ~~estradiol~~ and progesterone
 140 concentrations [(3, 4, 8)]. ~~It~~ ~~These findings~~ suggest ~~s~~ a luteolytic effect of the GnRH antagonist that
 141 ~~leads d~~ to ~~a decrease of~~ ~~reduced~~ ovarian activity and ~~secretion of~~ angiogenic factors ~~secretion~~,
 142 resulting in regression of severe OHSS [(4, 8)]. ~~GnRH antagonist inhibits M~~ ~~matrix metalloproteinase~~
 143 ~~(MMP)~~ and ~~therefore can, therefore,~~ disrupt ~~embryo the~~ implantation. ~~GnRH antagonist effect on~~
 144 ~~affects~~ the expression of *HOXA10* genes in ~~the~~ endometrium, which is an important regulator of
 145 endometrial receptivity² ([16]).

146 GnRH antagonist administration during ~~the~~ peri-implantation period may cause some concerns ~~about~~
 147 ~~regarding their~~ potential adverse effects ~~of GnRH antagonist~~ on embryo implantation, ~~and~~ pregnancy
 148 and neonatal outcomes ([11]). Our findings ~~showed~~ ~~revealed~~ that ~~the~~ pregnancy rate ~~is~~ ~~was~~ similar
 149 between ~~the~~ two ~~studied~~ ~~study~~ groups. ~~There are~~ ~~A~~ few studies ~~have about~~ ~~reported on~~ the effect of
 150 ~~luteal phase~~ GnRH antagonist ~~administration during the administration~~ ~~luteal phase~~ on pregnancy
 151 outcomes ([8, 11, 12]). Lainas *et al.*, in a prospective cohort study on 192 IVF patients, who were at
 152 risk of OHSS, ~~showed~~ ~~reported~~ that ~~pregnancy and neonatal outcomes~~ did not decrease after ~~luteal~~
 153 GnRH antagonist ~~administration during the luteal phase~~ ~~administration~~ ([1]). Some recent studies
 154 ~~have~~ documented that GnRH antagonist administration is not associated with pregnancy or
 155 congenital adverse effects ([1-4, 8-11, 17-20]).

Commented [49]: The original had an awkward and rather long *noun string*. As its name suggests, noun strings are strings containing several nouns in a single sentence, placed one after the other. This makes it difficult to comprehend the information. It is better to break this string down and rephrase the text in a way that improves clarity and enhances understanding. Please check my changes in this regard made here.

Commented [50]: Some conventions differ between British and American writing. One of these differences can be found in the spelling of certain words. For example, "flavor" in American English is spelt as "flavour" in British English. Some other examples are
 American English: color
 British English: colour
 American English: anemia
 British English: anaemia
 It's always a good idea to refer to a dictionary to find the most suitable spelling for your document. You can refer to Merriam Webster's for American English and Oxford Dictionary for British English, among others.

Commented [51]: The original idea was incomplete. Please review my addition.

Commented [52]: The original statement appeared incomplete as the effect was not described as such. I have rephrased the sentence to ensure completeness of the idea presented. Please review.

Commented [53]: Even when the original study is cited, quoting directly from a previous study is discouraged. I have, thus, edited the statements for grammar and clarity and removed the quotation marks.

Commented [54]: Do you mean "successful/positive pregnancy and neonatal outcomes"? Alternatively, do you mean "pregnancy and neonatal outcomes did not worsen"?

Commented [55]: Twenty references have been cited consecutively in the manuscript.

Commented [56]: Since several comparable studies are cited, it may be a good idea to elaborate on their findings with respect to those of this study. Were the findings exactly the same? In what ways were these different from the current study?

156 This study has some limitations. First, ~~As our study limitations,~~ OHSS evolution and ~~neonate~~
 157 ~~outcomes in neonates~~ and children ~~outcomes~~ were not studied. Furthermore, ~~Also the follow-follow-~~
 158 ~~up period was very short.~~

159 Conclusion

160 In conclusion, ~~luteal phase~~ GnRH antagonist administration ~~during the luteal phase~~ does not
 161 ~~affect/influence~~ the ~~chance/probability~~ of pregnancy after ~~assisted reproductive technology~~ ART. The
 162 incidence of chemical and clinical pregnancy ~~in groups~~ was not significantly different ~~among patients~~
 163 ~~who received GnRH antagonist during the luteal phase and those who did not receive it.~~

164 Acknowledgements

165 This study was supported by Yazd Research and Clinical Center for Infertility, Shahid Sadoughi
 166 University of Medical Sciences, Yazd, Iran.

167 Conflicts of Interest

168 The authors declare that there were no conflicts of interests regarding the publication of this article.

169 References

- 170 1. Lainas GT, Kolibianakis EM, Sfontouris IA, Zorzovilis IZ, Petsas GK, Tarlatzi TB, et al.
 171 Outpatient management of severe early OHSS by administration of GnRH antagonist ~~in the luteal~~
 172 ~~phaseduring the luteal phase~~: an observational cohort study. *Reprod Biol Endocrinol.* 2012;10: ~~69-71-~~
 173 ~~71.-~~
- 174 2. Lainas G, Kolibianakis E, Sfontouris I, Zorzovilis I, Petsas G, Lainas T, et al. Pregnancy and
 175 neonatal outcomes following luteal GnRH antagonist administration in patients with severe early
 176 OHSS. *Hum Reprod.* 2013;28:1929–1942.-

Commented [57]: There is a potential to improve this subsection of the discussion section. All elements of the limitations need to be highlighted, including the measures taken, if any, to avoid those limitations, and ideas stemming from the limitations for future studies.

Commented [A58]: As flagged in the abstract, your conclusions should be restricted to the antagonist studied.

Commented [59]: This abbreviation has been only used once in the main text. Per the guidelines, I have replaced this abbreviation with its expanded form.

Commented [A60]: Please considering discussing the implications and applications of these findings in the clinical field at large.

Commented [61]: This section is not required by the journal and may be deleted. The competing interests need to be provided via the submission system and should not be included in the manuscript.

Commented [62]: Please note that there are conflicting instructions in the guidelines for reference formatting. Examples of the format to be followed for references are provided on the journal page, and the instructions also mention that the journal follows the style outlined in the ICMJE sample references. These follow a slightly different style from that followed by the references on the journal page. I have followed the following instruction on the main journal formatting guidelines page:
 Hou WR, Hou YL, Wu GF, Song Y, Su XL, Sun B, et al. cDNA, genomic sequence cloning and overexpression of ribosomal protein gene L9 (rpl9) of the giant panda (*Ailuropoda melanoleuca*). *Genet Mol Res.* 2011;10: 1576-1588.

Devaraju P, Gulati R, Antony PT, Mithun CB, Negi VS. Susceptibility to SLE in South Indian Tamils may be influenced by genetic selection pressure on TLR2 and TLR9 genes. *Mol Immunol.* 2014 Nov 22. pii: S0161-5890(14)00313-7. doi: 10.1016/j.molimm.2014.11.005.

Note: A DOI number for the full-text article is acceptable as an alternative to or in addition to traditional volume and page numbers. When providing a DOI, adhere to the format in the example above with both the label and full DOI included at the end of the reference (doi: 10.1016/j.molimm.2014.11.005). Do not provide a shortened DOI or the URL.

Commented [63]: The citation in PubMed lists the page number as just 69. Please check this.

-
- 177 3. Lainas T, Sfontouris I, Zorzovilis I, Petsas G, Lainas G, Kolibianakis E. Management of severe
178 early ovarian hyperstimulation syndrome by re-initiation of GnRH antagonist. *Reprod Biomed*
179 *Online*. 2007;15: 408--412.-
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182 protocol. *Reprod Biomed Online*. 2009;18: 15--20.
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184 *Reprod*. 2002;17: 874--885.
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186 releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH
187 antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian
188 hyperstimulation syndrome: a prospective randomized controlled study. *Fertil Steril*. 2008;89: 84--
189 91.
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238 **Tables**

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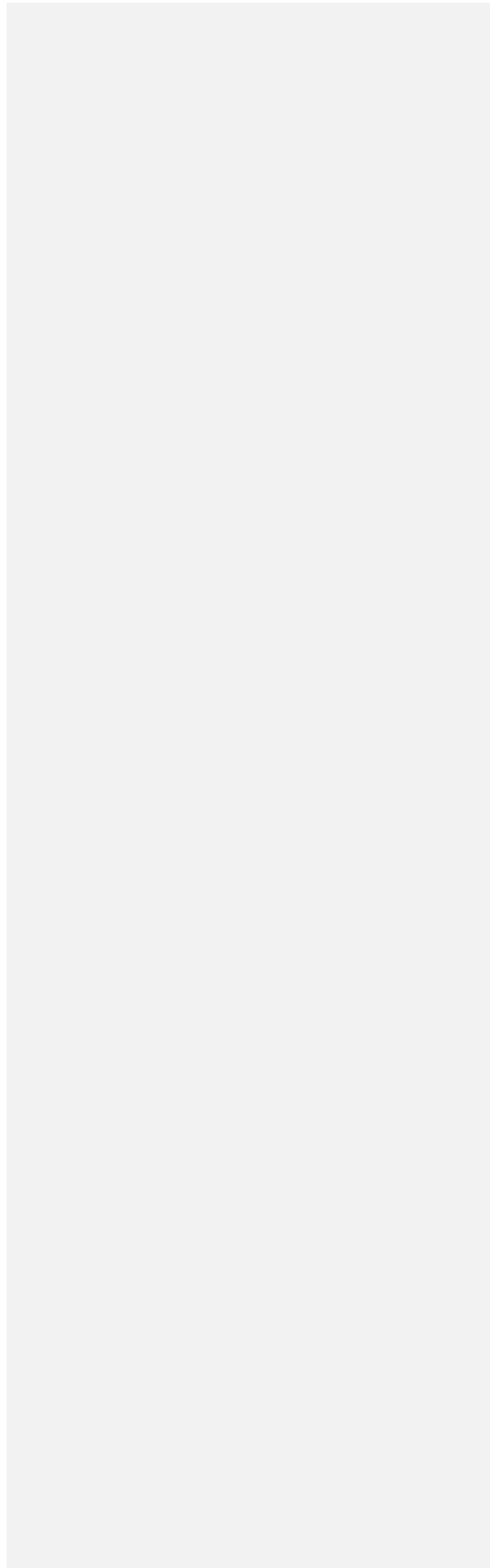
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Page 3: [1] Commented [_26]

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A compound adjective is formed by two words that jointly describe a noun (e.g., 'water' and 'soluble' in 'water-soluble compound'). Such compound adjectives are usually hyphenated to indicate that they form a single unit. The use of the hyphen also aids clarity. For example, in the sentence 'I saw a man-eating alligator,' it is clear that the alligator eats humans. Without the hyphen, the sentence will read as 'I saw a man eating alligator' (i.e., the man was eating an alligator).

Here, “cost effective” is the compound adjective to the noun “protocol”; therefore, it needs to be hyphenated.

Page 3: [2] Commented [_27]

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Please note that the reference number order will change if this change is made.

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The research rationale needs to be better formulated. In lines 45-48, you report the benefits of GnRH antagonists on IVF/ICSI cycles outcomes. You then state that the effects remain controversial. Where does the controversy reside? Could you cite reports with opposing results to those of the studies cited in lines 45-48?