PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.
AUTHORS	Issanov, Alpamys; Aimagambetova, Gulzhanat; Terzic, Sanja; Bapayeva, Gauri; Ukybassova, Talshyn; Baikoshkarova, Saltanat; Utepova, Gulnara; Daribay, Zhanibek; Bekbossinova, Gulnara; Balykov, Askhat; Aldiyarova, Aidana; Terzic, Milan

VERSION 1 – REVIEW

REVIEWER	Bahadur, Gulam North Middlesex University Hospital, Reproductive Medicine Unit
REVIEW RETURNED	08-Mar-2021

GENERAL COMMENTS	The paper is important and much work has gone into this analyse. However, there are several deficits which suggest a complete re-write is necessary to draw the multiple faceted issues relating to IVF outcomes and then depression. Ideally both could have been separate topics as they are both topics are interesting in their own rights. The title says nothing about the psychological/depression aspect and this is really another question. The content needs to be streamlined while the title should reflect the content. This study aimed to explore whether public funding is associated with less psychological distress for women undergoing in-vitro fertilization (IVF) treatment, whether public funding and clinical setting are independently associated with IVF outcomes, and whether publicly funded women have different IVF success rates depending on the type of clinical setting. In reality they have asked 3 questions. I am still struggling with the trueness of the prospective study as they have explained private clinic results could be explained by some selection bias. What exactly is oral consent and how is this proven? Its only when you reach page 6 does depression become important and actually interesting. Table 3: Most women were treated with short or long classic protocol, and pregnancy rate reached 62.2%. It needs to be made clear this is cumulative preg rate. What is preg rate per cycle? More importantly, what is the live birth rate? Success of private clinics is due to high numbers of oocytes being collected. If the selection bias is removed there would be true randomisation and therefore would the number of oocytes collected in private clinics be lower? Data analyses bias risk is high. The data on IVF outcomes were unknown for 22% of the study participants and this appears too high. On the second major subject of infertility related stress scores in social concern, sexual concern, relationship concern and global stress subscales were statistically significantly higher among women in the private clinics. Oddly, it is unclear how

	fee paying and failure anxiety contributed to the stress. Strictly, stress is not an outcome of IVF like birth rates, but an association of IVF related procedures. Their conclusion that high prevalence of depression and anxiety among IVF patients than the general population is not supported by a control group. As the paper talks about funding they need to include https://bmjopen.bmj.com/content/10/3/e034566 and state other treatment options such as IUI is available which is cost effective and less risky. The paper has importance and the authours need to completely re-write the paper overcoming some of the concerns highlighted.

REVIEWER	Chambers, Georgina University of New South Wales, Achool of Women's and Children's Health
REVIEW RETURNED	18-Mar-2021

GENERAL COMMENTS	This study evaluates the association between 1) public and private IVF clinics and 2) Publicly funded or self-pay arrangement on 3) psychological stress and clinical pregnancy rates. Its an important and novel topic and I agree with the authors that effect of the type of IVF clinic on clinical and psyc outcomes have not be directly evaluated in a systematic way. The results suggest that depression is higher in private clinics and self-funded patients. BUT clinical pregnancy is higher in public patients and self-funded patients. Overall Comment. It an interesting paper but covers a lot of interacting exposures and outcomes, and this has multiple comparisons, plus tests for effect modification. The seemingly contradictory findings for some of the associations need to be more clearly presented. I would strongly suggest just focusing on one outcome: clinical pregnancy or psychological, to make the results clearer. Two manuscripts would be my suggestion, My comments are: 1. The Abstract needs to be clearer and include number of patients etc, and that IVF funding type can occur in both clinic types (public and private). 2. Introduction: There are four complex aims stated in the Introduction. These are difficult to digest. I don't even think Aim one is really addressed – I think that's covered the author's previous paper. 3. The references in the introduction should be improved, and I suggest doing a review of the literature – e.g. see work by authors like: Hamilton, B.H., McManus, B. The effects of insurance mandates on choices and outcomes in infertility treatment markets. Health Econ. 2012; 21: 994–1016 Chambers, G.M., Hoang, V.P., Sullivan, E.A., Chapman, M.G., Ishihara, O., Zegers- Hochschild, F., Karl, G., Nygren, K.G., Adamson, G.D. The impact of consumer affordability on access to assisted reproductive technologies and embryo transfer practices: an international analysis. Fertil. Steril. 2014; 101. Peterson, B.D., Sejbaek, C.S., Pirritano, M., Schmidt, L Are severe depressive symptoms associated with infertility-related distress in individuals and their partners. Hum. Reprod. 2014; 29: 76–82

	Präg, P., Mills, M. Cultural determinants influence assisted reproduction usage in Europe more than economic and demographic factors. Hum. Reprod. 2017; 32: 2305–2314 And I don't see how reference 6 is valid for all citations where it is mentioned. The authors also need to reference primary sources. How do long-term financial benefits occur from citizens' meeting the basic need of parenthood? 4. Make sure describe the setting of public and private, govt funded and self-funded more clearly. 5. Methods: These seem ok, if not brief. 5. Results: The first four tables a decription of the cohorts sliced different ways. If you stick to one outcome of one exposure this could be simplified. Do you have any diagnostics on how well you model fitted the data (Table 5) The analysis of the interaction (modifying effect of payment type on clinical setting) should be shown). It seems surprising there was no interaction. Were there other interactions? It would be important to report on multiple birth rates b/w the settings and payer types. Can this be done? 6. Perhaps to make the results clearer, could the authors explore using visualization. Manuscripts with multiple comparison and dense tables are difficult to comprehend for the average reader. 7. Discussion: again a lot is covered here (both clinical outcomes and pscyh outcomes with multiple exposures being tested) and some appears contradictory. Eg State funding increased access to IVF of poor prognosis women, line 15, but these have a higher chance of conceiving a child (line 55). Also there is evidence that good prognosis and poor prognosis (bimodal) tend to access RX when it is more affordable because the balance b/w cost and benefit is reduced for both population of women. Again, in summary I would suggest focusing on one outcome (in my opinion the IVF treatment outcomes first) and splitting the paper into two manuscripts with clear aims. I hope the authors resubmit this interesting work after making modifications.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1 comments
1) The paper is important and much work has gone into this analyse.

Authors' reply: We thank Dr. Gulam Bahadur for spending time reviewing our manuscript.

2) However, there are several deficits which suggest a complete re-write is necessary to draw the multiple faceted issues relating to IVF outcomes and then depression. Ideally both could have been separate topics as they are both topics are interesting in their own rights.

Authors' reply: We greatly appreciate the comment. After careful reconsideration, we agree that the manuscript contained too much information. Thus, we decided to focus on one aim, reanalyzed data, and reframed the manuscript.

3) The title says nothing about the psychological/depression aspect and this is really another question. The content needs to be streamlined while the title should reflect the content.

Authors' reply: We thank the Reviewer for this comment. After careful reconsideration, we decided to focus on one aim and to focus on the relationship of IVF outcomes with clinical settings and payment type while leaving out psychological factors from this manuscript. We will write a separate manuscript discussing an association between clinical settings and psychological factors. Now, we believe the title reflects the updated content in the manuscript.

4) This study aimed to explore whether public funding is associated with less psychological distress for women undergoing in-vitro fertilization (IVF) treatment, whether public funding and clinical setting are independently associated with IVF outcomes, and whether publicly funded women have different IVF success rates depending on the type of clinical setting. In reality they have asked 3 questions.

Authors' reply: Yes, we agree that the manuscript was overloaded with aims and presented analysis results. Thus, we focused on one research question, reanalyzed data, and reframed the manuscript.

5) I am still struggling with the trueness of the prospective study as they have explained private clinic results could be explained by some selection bias.

Authors' reply: We appreciate the Reviewer's comment in this regard. Given a study design limitation, we were not able to randomly select participants, instead, we used a non-random convenient sampling technique. And we acknowledged this limitation in the discussion saying that we were not able to compare non-respondents to respondents to exclude non-response bias. However, we took all possible measures to reduce selection bias in all clinical settings when recruiting patients into the study. All participants meeting inclusion criteria and those who provided written informed consent were included. Inclusion was not based on participants' better reproductive prognosis in any clinical settings. The observed difference in the number of oocytes retrieved between private and public clinics is not related to the study limitation, but rather peculiarities of selecting patients for IVF treatment in certain clinical settings. In order to obtain more robust results, we excluded one private clinic with a very high pregnancy rate. The results of the sensitivity analysis were no different from the findings from the whole cohort.

6) What exactly is oral consent and how is this proven?

Authors' reply: We apologize for this mistake in the text. What we meant is that all participants were asked to sign a written informed consent form. If they had questions about the study, researchers verbally provided explanations. We made changes accordingly in the text.

7) Its only when you reach page 6 does depression become important and actually interesting.

Authors' reply: Because the manuscript was overloaded with aims and analysis, we decided to focus on the relationship of IVF outcomes with clinical settings and payment type while leaving out psychological factors from this manuscript. We will write a separate manuscript discussing an association between clinical settings and psychological factors. Now, we believe the title reflect the updated content in the manuscript. Hope you will find the update manuscript also interesting.

8) Table 3: Most women were treated with short or long classic protocol, and pregnancy rate reached 62.2%. It needs to be made clear this is cumulative preg rate.

Authors' reply: We thank the Reviewer for this comment. We indicated in the manuscript that this is the cumulative pregnancy rate.

9) What is preg rate per cycle? More importantly, what is the live birth rate?

Authors' reply: Unfortunately, we did not collect this data and are not able to provide statistics about them.

10) Success of private clinics is due to high numbers of oocytes being collected. If the selection bias is removed there would be true randomisation and therefore would the number of oocytes collected in private clinics be lower?

Authors' reply: We could speculate that if private clinics were not selecting patients based on their reproductive prognosis characteristics, then the numbers of oocytes retrieved in public and private sectors would be comparable to each other. Despite that the number of oocytes retrieved is strongly associated with IVF outcomes, we found that the clinical setting itself was an independent predictor. We hypothesized that the greater number of oocytes retrieved would play a role as a mediator between the relationship of IVF outcomes and private clinics, as the greater number of oocytes retrieved would likely be associated with higher IVF success rates. However, inclusion both of the number of oocytes retrieved and the clinical setting in the model revealed that the clinical setting was independently statistically significantly associated with the IVF outcomes while the number of oocytes retrieved became non-significant. It means that private clinics on their own had other factors that contributed to better IVF outcomes, other than the number of oocytes being collected.

11) Data analyses bias risk is high. The data on IVF outcomes were unknown for 22% of the study participants and this appears too high.

Authors' reply: We acknowledged in the limitations that we had a high proportion of missing data about IVF outcomes. There is a debate on what proportion of missing data should be considered acceptable. Some researchers suggested that 40% or above are likely to produce biased estimates while 5% or less % of missing data do not distort overall results (J.C. Jakobsen, C. Gluud, J. Wetterslev, P. Winkel When and how should multiple imputations be used for handling missing data in randomised clinical trials–a practical guide with flowcharts BMC Med Res Methodol, 17 (2017), p. 162.). However, it is, more importantly, to know what mechanisms and patterns that generate missing data. We assumed that missing data were completely at randomly generated given that patients with missing data were not demographically statistically significantly different. Since the data were missing completely at random, it is not generally recommended to use data imputations. So, we decided to perform a complete case analysis based on the available data.

12) On the second major subject of infertility related stress scores in social concern, sexual concern, relationship concern and global stress subscales were statistically significantly higher among women in the private clinics. Oddly, it is unclear how fee paying and failure anxiety contributed to the stress. Strictly, stress is not an outcome of IVF like birth rates, but an association of IVF related procedures.

Authors' reply: We thank the Reviewer for the comment. Since we restructured the manuscript, psychological factors are not anymore discussed. Please see the updated manuscript.

13) Their conclusion that high prevalence of depression and anxiety among IVF patients than the general population is not supported by a control group.

Authors' reply: We thank the Reviewer for the comment. Since we restructured the manuscript, psychological factors are not anymore discussed. Please see the updated manuscript.

14) As the paper talks about funding they need to include https://bmjopen.bmj.com/content/10/3/e034566 and state other treatment options such as IUI is available which is cost effective and less risky.

Authors' reply: We appreciate the suggested citation. We included it in the discussion part. "Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has been shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.34"

15) The paper has importance and the authors need to completely re-write the paper overcoming some of the concerns highlighted.

Authors' reply: We greatly appreciate your time and efforts put into the review. Based on your valuable comments, we restructured the manuscript and narrowed the focus. Particularly, we removed all analyses and discussions related to psychological factors, as we will write a different manuscript on this topic. We believe now the manuscript is more focused and clear. Hope you will find the updated manuscript interesting.

Reviewer #2 comments

1) This study evaluates the association between 1) public and private IVF clinics and 2) Publicly funded or self-pay arrangement on 3) psychological stress and clinical pregnancy rates. Its an important and novel topic and I agree with the authors that effect of the type of IVF clinic on clinical and psyc outcomes have not be directly evaluated in a systematic way.The results suggest that depression is higher in private clinics and self-funded patients. BUT clinical pregnancy is higher in public patients and self-funded patients.

Authors' reply: We thank Dr. Georgina Chambers for spending time reviewing our manuscript and providing valuable comments.

2) It an interesting paper but covers a lot of interacting exposures and outcomes, and this has multiple comparisons, plus tests for effect modification. The seemingly contradictory findings for some of the associations need to be more clearly presented. I would strongly suggest just focusing on one outcome: clinical pregnancy or psychological, to make the results clearer. Two manuscripts would be my suggestion.

Authors' reply: We highly appreciate this comment. After reconsidering the manuscript, we agreed with the Reviewer. The aim of the study was limited to only one related to the title, data was reanalyzed and the manuscript was rewritten.

3) The Abstract needs to be clearer and include number of patients etc, and that IVF funding type can occur in both clinic types (public and private).

Authors' reply: We updated the abstract according to the comment. Also changes were made based on revision of the main text.

4) Introduction: There are four complex aims stated in the Introduction. These are difficult to digest. I don't even think Aim one is really addressed – I think that's covered the author's previous paper.

Authors' reply: We appreciate this valuable comment by the Reviewer. After careful reconsideration, we decided to focus on one aim and to investigate the relationship of IVF outcomes with clinical settings and payment type while leaving out psychological factors from this manuscript.

5) The references in the introduction should be improved, and I suggest doing a review of the literature – e.g. see work by authors like:
Hamilton, B.H., McManus, B. The effects of insurance mandates on choices and outcomes in infertility treatment markets. Health Econ. 2012; 21: 994–1016
Chambers, G.M., Hoang, V.P., Sullivan, E.A., Chapman, M.G., Ishihara, O., Zegers- Hochschild, F., Karl, G., Nygren, K.G., Adamson, G.D. The impact of consumer affordability on access to assisted reproductive technologies and embryo transfer practices: an international analysis. Fertil. Steril. 2014; 101.
Peterson, B.D., Sejbaek, C.S., Pirritano, M., Schmidt, L Are severe depressive symptoms associated with infertility-related distress in individuals and their partners. Hum. Reprod. 2014; 29: 76–82
Präg, P., Mills, M. Cultural determinants influence assisted reproduction usage in Europe more than economic and demographic factors. Hum. Reprod. 2017; 32: 2305–2314

Authors' reply: We thank the Reviewer for this comment. We performed additional literature review and added references in the introduction section. Please see highlighted changes in the manuscript.

6) And I don't see how reference 6 is valid for all citations where it is mentioned. The authors also need to reference primary sources.

Authors' reply: We revised and updated the reference list in the manuscript.

7) How do long-term financial benefits occur from citizens' meeting the basic need of parenthood?

Authors' reply: We apologize for the confusing sentence. We rephrased it. Please see highlighted changes in the manuscript.

8) Make sure describe the setting of public and private, govt funded and self-funded more clearly.

Authors' reply: We added more information about clinical setting and funding. Please see changes highlighted in the "Study design" section in the methods part.

9) Methods: These seem ok, if not brief.

Authors' reply: We expanded the study variables subsection in the methods part.

10) Results: The first four tables a description of the cohorts sliced different ways. If you stick to one outcome of one exposure this could be simplified.

Authors' reply: We thank the Reviewer for the comment. We narrowed the focus of the manuscript and changed the tables so it is easier to follow.

11) Do you have any diagnostics on how well you model fitted the data (Table 5)

Authors' reply: We examined goodness-of-fit of the final models using Pearson's and deviance goodness of fit tests. The goodness-of-fit statistics were non-significant indicating that the models fitted well enough the sample data.

12) The analysis of the interaction (modifying effect of payment type on clinical setting) should be shown). It seems surprising there was no interaction. Were there other interactions?

Authors' reply: Despite the interaction between payment type and the clinical setting was non-significant, we presented results in Table 5. We speculate that the non-significant finding could be

attributed to the low sample size. Additionally, we checked for the existence of other interactions. The interaction between comorbidity and the clinical setting was found statistically significant. Please see highlighted updates in the statistical analysis subsection in the manuscript.

13) It would be important to report on multiple birth rates b/w the settings and payer types. Can this be done?

Authors' reply: We performed additional analysis and included statistics on multiple pregnancies. Please see the Tables and changes highlighted in the text. Overall, private clinics had a higher number of multiple pregnancies than public clinics due to the greater number of embryos transferred in their settings.

14) Perhaps to make the results clearer, could the authors explore using visualization. Manuscripts with multiple comparison and dense tables are difficult to comprehend for the average reader.

Authors' reply: We appreciate the comment. We removed some of the tables and simplified some of them. Hope you will find the tables easier to read.

15) Discussion: again a lot is covered here (both clinical outcomes and pscyh outcomes with multiple exposures being tested) and some appears contradictory. Eg State funding increased access to IVF of poor prognosis women, line 15, but these have a higher chance of conceiving a child (line 55). Also there is evidence that good prognosis and poor prognosis (bimodal) tend to access RX when it is more affordable because the balance b/w cost and benefit is reduced for both population of women.

Authors' reply: We thank the Reviewer for this comment. We removed the mentioning that state funding increased access to IVF for poor prognosis women in that context as it was not appropriate, and indeed contradicting. However, later we stated that in Kazakhstan there is still limited access to IVF, and in order to receive public funding women need to go through a very rigorous selection process. Women with better prognoses usually are selected. That is why our findings concerning the relationship between public funding and IVF outcomes are inconsistent with previous findings. Please see the changes highlighted in the text.

16) Again, in summary I would suggest focusing on one outcome (in my opinion the IVF treatment outcomes first) and splitting the paper into two manuscripts with clear aims. I hope the authors resubmit this interesting work after making modifications.

Authors' reply: We sincerely appreciate your time put into this review and your feedback. Based on your valuable comments, we restructured the manuscript and narrowed the focus. Particularly, we removed all analyses and discussions related to psychological factors, as we will write a different manuscript on this topic. We believe now the manuscript is more focused and clear. Hope you will find the updated manuscript interesting.

VERSION 2 – REVIEW

REVIEWER	Bahadur, Gulam North Middlesex University Hospital, Reproductive Medicine Unit
REVIEW RETURNED	22-May-2021

GENERAL COMMENTS	Impact of governmental support to the IVF outcome: differences between public and private clinical settings in Kazakhstan. A prospective cohort study.

	Utilization of governmental support of IVF procedures This is an improved resubmission but considerable works still need to be performed. The removal of depression/stress analyses is very important and needs to be a separate paper This is not a prospective cohort study. With funding needs comes the cost effectiveness analyses see Bahadur et al which recommendation they need to reconsider its inclusion. They need to analyse and include https://bmjopen.bmj.com/content/10/3/e034566. This is because the hub of the paper centres around funding. The reference considers other treatment options such as IUI against IVF finding IUI to be cost effective and less risky. Importantly this analysis can be replicated to their scenario and compare cost effectiveness between 2 domains of treatments. Overall, the paper comes across as `speaking to their funding agency' to provide more funded treatment cycles and they propose to provide evidence through this paper? Some subliminal marketing bias with their government/fee paying agency as their audience. The flaws are thus; These is a tenuous association of success as none of their data actually shows the benefits. It appears not special skills to impregnate a woman with more oocytes and end up with higher risk babies. While it may appear and I have not checked to be the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings, there are huge weaknesses. They are relying on statistical modelling independent relationships of the clinical settings and payment type with the IVF outcomes, but what could matter most is cost effective analyses as suggested above. There was huge non-response rate (85%) which is uncomfortable as to why people are not responding. Is it because of failure rate and hence what we looking at is an extremely biased picture? They will already have a clue from their records of the level of pregnancies? In this sense I did ask to clarify what they meant by success rates? How would a private IVF clinic not know the outcomes for 22% on top of the low response of the study participants. Low ovarian reserve do not fall under the government support and this creates a bias in favour of private clinics. The fact is that statistically significantly more eggs are collected in the private sector than public sector which speaks of the ovarian reserve favourabe for the private sector, as does the high multiple births in the private sector. There is a negative point for the private sector and the cost burden of multiple births is lost to account. I have never seen a disparity of success rates. It speaks of clinical pregnancy rate (of what?) as 29.7% versus 79%. The multiple birth rate for such level of multiple embryo transfer of 1.4 % seems not credible unless This seems not credible when comparing clinics across nations. The cost of drugs will have increased in the private clinics. A significant area could have been addressed with ICER cost effective analyses as suggested in the reference above. This simplified paper allows a more critical analyses of the deficits of this paper. Perhaps the authours can refute these analyses and perfom ICER analyses

	This study aimed to explore whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type. To some extent this question is answered but through questionable and weak methodology and interpretations

REVIEWER	Chambers, Georgina University of New South Wales, Achool of Women's and Children's Health
REVIEW RETURNED	03-Jun-2021

GENERAL COMMENTS	I am pleased that the authors have simplified the aims of this study to now investigate clinical pregnancy rates between private and public IVF clinics and the role of public versus self funded treatment. However, the manuscript still requires some work before it is ready for publication. I also suggest an English language edit be performed. My comments are: Title: The title should reflect the study. IVF outcomes should be replaced with clinical pregnancy rates and both setting and funding models were investigated. Abstract – Must include that only 14% of women participated in 5 of x clinics operation in the country and missing outcome data on 22%. The conclusions are too far reaching, in that only clinical pregnancy rates are measured, and not Live birth rates or multiple birth rates. Success rates are more about singleton live births. If one setting is producing high twin and triplet, this would change the conclusions about 'success' Strengths and weaknesses - Im not sure this is the first study to investigate public versus provide – I would be surprised if it was. - Still references to psychological status I believe France and Israel and maybe Spain to have limits on the number of cycles funded based on no. of children or number of previous failed attempts. Methods The outcome is clinical pregnancy. I would make this clear. But also is it clinical pregnancy per egg retrieval cycle (cumulative fresh and frozen from one egg retrieval)? How long was the followup? Did private patients do more or less embryos transfer procedure per egg retrieval compare to public patients? Please define this carefully because it makes a big difference to how the results are interpreted. The fact that on average 2 embryos were transferred each cycle makes is hard to believe the multiple pregnancy rates of 1%, this can't be right. Also, is clinical pregnancy rate per number of embryos transferred the implantation rate? It was double in private clinics. Why would this be? I think this is a key finding of the paper. I do not think no. of oocytes is an outcome in its own right. This can be in the causal pathway and can be a direct effect of the approach to stimulation. If you consider it in the causal pathway, it arguably should not be controlled for either in your models. Results Can you present the regression analysis in a more traditional format please showing the reference and crude and adjusted

	measures relative to this, so the reader can see how each variable contributed to the results. Adding a lay interpretation of the interaction is need. I suggest asking a biostatistician to assist with the analysis and presentation. The general methods are appropriate but advice on the model specification and presentation are needed. Discussion There appear to still be contradictions the role that prognosis of the patients play. It appears from the text that public funding is made available to those with a good prognosis, but then it is said that private clinics choose good prognosis patients. Can you please make this clear? There is a lot and of missing data and we have no way of knowing whether this is truly missing at random – only that equal proportions were missing from public and private clinics. Thus don't agree with your point on page 13. It would be very nice to see this paper published and I encourage the authors to keep working on it, but the analysis needs to be correct, limitations made clear, and conclusions only reflect results.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 comments:

1) This is an improved resubmission but considerable works still need to be performed. The removal of depression/stress analyses is very important and needs to be a separate paper

Authors' reply:

Thank you for your time reviewing the revised manuscript. We appreciate your previous and current comments that helped to substantially improve the manuscript.

2) This is not a prospective cohort study.

Authors' reply:

We believe that this is a prospective cohort study, as we recruited women attending IVF clinics prior any procedures were performed and regardless of their clinical outcomes. In contrast to case-control or cross-sectional studies, we enrolled participants from a cohort without knowing the outcomes and followed them through until the outcomes occur. Thus, we believe the current study design falls under the description of a prospective cohort study.

3) With funding needs comes the cost effectiveness analyses see Bahadur et al which recommendation they need to reconsider its inclusion. They need to analyse and include https://bmjopen.bmj.com/content/10/3/e034566. This is because the hub of the paper centres around funding. The reference considers other treatment options such as IUI against IVF finding IUI to be cost effective and less risky. Importantly this analysis can be replicated to their scenario and compare cost effectiveness between 2 domains of treatments.

Authors' reply:

Thank you for this comment. It is absolutely true that IUI is less risky and much cheaper intervention than IVF. Patients recruited in our study had indications for IVF approach, while insemination as a procedure remained far below and behind it. The mentioned study published in BMJ open and written by Bahadur et al. uniquely described comparative treatment outcomes of IVF/ICSI and IUI, multiple birth risks, cost implications, including cost to achieve a live birth and of neonatal costs in the UK. Their goal was different from ours, aiming to explore whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type. Regarding cost implications, we cited the proposed reference in our discussion:

"Self-paid patients and the government could consider other alternative fertility options. Intrauterine insemination could be an alternative fertility treatment as it has been shown to be more cost-effective and associated with lower risks, and most importantly its success rate is quite comparable to IVF treatment.[34]"

4) Overall, the paper comes across as `speaking to their funding agency' to provide more funded treatment cycles and they propose to provide evidence through this paper? Some subliminal marketing bias with their government/fee paying agency as their audience.

Authors' reply:

We appreciate the Reviewer for raising this concern. One of the aims of the research was to draw attention to the existing high demand for IVF treatment through public funding in Kazakhstan as there are a lot subfertile low-income couples who are not able to receive the treatment because of the strict selection criteria. As a result, women with better prognosis are usually selected – "skimming the cream off the milk". We discuss that increasing the public funding, which has, in fact, been already implemented (the number of the public quotes increased seven times), will likely see lowering IVF success rates than before. And it is recognized international practice. The availability of public funding will allow couples with less favorable prognosis to be enrolled while giving them opportunity to conceive their child.

5) The flaws are thus;
These is a tenuous association of success as none of their data actually shows the benefits. It appears not special skills to impregnate a woman with more oocytes and end up with higher risk babies.

Authors' reply:

We do understand that uncovering associations in observational studies are challenging, as results could be confounded and/or biased. In order to avoid or minimize confounding and bias, we implemented the multiple regression analyses. We agree that the number of oocytes retrieved and number of embryos transferred are strong predictors for the clinical pregnancy. In drawing a directed acyclic graph for the relationship between clinical settings or funding models with the clinical pregnancy, we identified that these both variables were mediators (as they stood in the unidirectional path between an exposure and the outcome). Our initial thought was to not include it in the multiple regression modeling. However, we understood if we did not adjust for them, we would not know whether observed differences between clinicals settings or funding models were solely attributed to how many oocytes retrieved or how many embryos transferred or actually there could be other indirect paths that could explain the relationship. After adjusting, we believe we underlined the existence of other factors that potentially contribute to better outcomes for private clinics (more experienced embryologists, quality embryos, and other factors) and for publicly funded women (selection of patients with better reproductive prognosis). Thus, we decided to include it in the models so to see whether other (unfortunately, not measured) factors within clinical settings or funding models are associated with the outcome.

6) While it may appear and I have not checked to be the first multicenter study investigating potential predictors for the IVF outcomes between private and public clinical settings, there are huge weaknesses.
They are relying on statistical modelling independent relationships of the clinical settings and payment type with the IVF outcomes, but what could matter most is cost effective analyses as suggested above.

Authors' reply:

Our apologies for causing confusion. What we meant that this is the first study in Kazakhstan. We changed it. The mentioned study published in BMJ open and written by Bahadur et al. uniquely described comparative treatment outcomes of IVF/ICSI and IUI, multiple birth risks, cost implications, including cost to achieve a live birth and of neonatal costs in the UK. Their goal was different from ours, aiming to explore whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type.

7) There was huge non-response rate (85%) which is uncomfortable as to why people are not responding. Is it because of failure rate and hence what we looking at is an extremely biased picture? They will already have a clue from their records of the level of pregnancies? In this sense I did ask to clarify what they meant by success rates?

Authors' reply:

We thank the Reviewer for this comment. It is undeniably a high non-response rate, and we acknowledge it in the study limitations section. We were able to enroll only 14% of the patients while following ethical principles of the Helsinki declaration and limiting any influence of physician-patient relationship. Because subfertile couples attending IVF clinics were likely experiencing psychological discomfort and under tremendous societal pressure, it was very important in our study to follow ethical standards in human research and do not cause additional psychological distress attending women. It is culturally accepted in Kazakhstan to have three or more children in a family. And couples with inability to conceive a child, especially women, can be treated with scorn, resulting in loneliness and stigmatization from family or relatives site (Tabyshalieva A. Women of Central Asia and the Fertility Cult, Anthropology & Archeology of Eurasia, 1997; 36:2:45–62. https://doi.org/10.2753/AAE1061-1959360245).

We also tried to compare the participants' demographic data with existing literature. However, there is limited data on demographical characteristics of women attending IVF clinics in Kazakhstan. A study conducted by Lokshin, NV. et al. found that more than half of women in IVF clinics were younger than 34 years old. Similar results were obtained in our study (50.3%).

Reference:
https://www.researchgate.net/publication/344712263_ASSISTED_REPRODUCTIVE_TECHNOLOGIES_IN_KAZAKHSTAN_IN_2017_SUMMARY_REPORT_ON_EFFICIENCY_AND_AVAILABILITY_ANNOTATION#fullTextFileContent

8) How would a private IVF clinic not know the outcomes for 22% on top of the low response of the study participants.

Authors' reply:

Due to COVID-19, it was not possible (and still it is challenging) to access patient follow-up data for 22% of the participants. We acknowledged this weakness in the discussion section.

9) Low ovarian reserve do not fall under the government support and this creates a bias in favour of private clinics.

Authors' reply:

Yes, this was on of the main findings of the study. Patients with low ovarian reserve are likely to pay out of pocket as the government does not support couples with lower probabilities of conceiving a child. On the other hand, private clinics try to select also patients with better prognosis or transfer more than one embryo so to increase chances of pregnancy.

10) The fact is that statistically significantly more eggs are collected in the private sector than public sector which speaks of the ovarian reserve favorable for the private sector, as does the high multiple births in the private sector. There is a negative point for the private sector and the cost burden of multiple births is lost to account.

Authors' reply:

We appreciate the comment. We added the following sentence in the discussion: "Multiple pregnancies are not only associated with higher risks of morbidity and mortality for mothers during pregnancy, (REF1) but also with greater total pregnancy costs, antenatal care and delivery costs when compared with singleton births.(REF2)"

1) Norwitz ER, Edusa V, Park JS. Maternal physiology and complications of multiple pregnancy. InSeminars in perinatology 2005 Oct 1 (Vol. 29, No. 5, pp. 338-348). WB Saunders.
2) Mistry H, Dowie R, Young TA, Gardiner HM, TelePaed Project Team. Costs of NHS maternity care for women with multiple pregnancy compared with high-risk and low-risk singleton pregnancy. BJOG: An International Journal of Obstetrics & Gynaecology. 2007 Sep;114(9):1104-12.

11) I have never seen a disparity of success rates. It speaks of clinical pregnancy rate (of what?) as 29.7% versus 79%.

Authors' reply:

Yes, it was a far large difference in clinical pregnancy rates between clinical settings than expected. Please see the distribution of clinical pregnancy rates among clinics by ownership type:

Private clinics:

Private Clinic (PC)	Clinical pregnancy		Total
	no	yes	
PC#1	38 (39.2)	59 (60.8)	97 (100)
PC#2	2 (1.9)	103 (98.1)	105 (100)
PC#3	8 (29.63)	19 (70.37)	27 (100)
Total	48 (21.0)	181 (79.0)	229 (100)

Public clinics:

Public clinic (PubC)	Clinical pregnancy		Total
	no	yes	
PubC#1	31 (54.4)	26 (45.6)	57 (100)
PubC#2	52 (85.2)	9 (14.8)	61 (100)
Total	83 (70.3)	35 (29.7)	118 (100)

As you may see the pregnancy rate in Private clinic#2 was suspiciously too high. Thus, it was decided to perform sensitivity analysis by excluding this clinic. We discuss this analysis in the discussion section: "To obtain more robust results, further sensitivity analysis was performed (Supplementary Table 7). To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis.[16] The sensitivity analysis revealed that the public clinics still were independently associated with lower clinical pregnancy rates across all multiple regression models, which were adjusted for the same covariates." The sensitivity analysis yielded the same results as with the total sample size.

We agree this discrepancy deserves further study, and we planned to perform it in the future as a part of thesis of our PhD candidate. It is well known that private clinics want to have higher IVF outcomes, and use this result for their advertising and marketing purposes. Higher pregnancy rate in private clinics might be related to different selection criteria for IVF procedure, and better knowledge and skills of physicians.

12) The multiple birth rate for such level of multiple embryo transfer of 1.4 % seems not credible unless This seems not credible when comparing clinics across nations. The cost of drugs will have increased in the private clinics.

Authors' reply:

Thank you for this comment. We found that private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2, p<0.001), transferred more embryos (2.2±2.5 vs 1.4±1.1, p<0.001), and had more multiple pregnancies (0 vs 4, p=0.32) than the public clinics (Table 3). Private clinics had statistically significantly higher cumulative pregnancy rate compared to the public clinics (79.0% vs 29.7%, p<0.001). As addressed in answer to previous question, these differences will be analyzed in the future, and might be related to both patients' and physicians' factors. For that, the costs of drugs in private clinics might not be ultimately significantly increased.

13) A significant area could have been addressed with ICER cost effective analyses as suggested in the reference above. This simplified paper allows a more critical analyses of the deficits of this paper. Perhaps the authors can refute these analyses and perform ICER analyses

Authors' reply:

We thank the Reviewer for the valuable suggestion. We would like to conduct a similar study as by Bahadur et al. did in the future. While our study has several limitations, we strongly believe it adds a scientific merit in drawing a picture of the relationships between clinical settings and funding types with IVF outcomes in Kazakhstan. And it will be a starting point for future research as there is a scarce of data in Kazakhstan and the Central Asian region.

14) This study aimed to explore whether public funding and clinical setting are associated with IVF outcomes, and to determine whether the relationship between IVF outcomes and clinical setting is modified by payment type. To some extent this question is answered but through questionable and weak methodology and interpretations

Authors' reply:

While our study has several limitations, we strongly believe it adds a scientific merit in drawing a picture of the relationships between clinical settings and funding types with IVF outcomes in Kazakhstan. And it will be a starting point for future research as there is a scarce of data in Kazakhstan and the Central Asian region.

Reviewer #2 comments:

1) I am pleased that the authors have simplified the aims of this study to now investigate clinical pregnancy rates between private and public IVF clinics and the role of public versus self funded treatment.

Authors' reply:

We thank the Reviewer taking time to review and providing valuable comments for the revised manuscript.

2) However, the manuscript still requires some work before it is ready for publication.
I also suggest an English language edit be performed.

Authors' reply:

Thank you for your suggestion. The manuscript went through English proofreading and was edited.

3) Title: The title should reflect the study. IVF outcomes should be replaced with clinical pregnancy rates and both setting and funding models were investigated.

Authors' reply:

We agree and changed the title accordingly. Now it is following: "Impact of governmental support to the IVF clinical pregnancy rates: differences between public and private clinical settings in Kazakhstan. A prospective cohort study."

4) Abstract – Must include that only 14% of women participated in 5 of x clinics operation in the country and missing outcome data on 22%.

Authors' reply:

We appreciate the comment. We made changes accordingly. Please see the abstract.

5) The conclusions are too far reaching, in that only clinical pregnancy rates are measured, and not Live birth rates or multiple birth rates. Success rates are more about singleton live births. If one setting is producing high twin and triplet, this would change the conclusions about 'success'

Authors' reply:

We thank the Reviewer for noticing this mistake. We changed the wording and made it clear that all conclusions are about clinical pregnancy rates.

6) Strengths and weaknesses
Im not sure this is the first study to investigate public versus provide – I would be surprised if it was.

Authors' reply:

Our apologies for causing confusion. What we meant that this is the first study in Kazakhstan. We changed it.

7) -Still references to psychological status

Authors' reply:

We are very grateful for catching and pointing at this. We removed any references to psychological status in our paper. See updated statement in the Strengths and limitations of this study section.

8) I believe France and Israel and maybe Spain to have limits on the number of cycles funded based on no. of children or number of previous failed attempts.

Authors' reply:

Dear Reviewer, thank you very much for your comments. In our manuscript we did not aim to specifically highlight how much funding some developed countries spent for ART support (and number of cycled covered), but to highlight that it is not affordable for the majority of low-income countries.

If to discuss the number of cycles that particular countries cover, we found Israeli National Health Insurance covers unlimited cycles of IVF for all Israeli women with up to two children in a given relationship, until the age of 45, even if the woman already has living children [Simonstein, F., Mashiach-Eizenberg, M., Revel, A., & Younis, J. S. (2014). Assisted reproduction policies in Israel: a retrospective analysis of in vitro fertilization–embryo transfer. Fertility and Sterility, 102(5), 1301–1306. doi:10.1016/j.fertnstert.2014.07.740***].***

Spain and France provide full coverage of IVF treatments as a matter of policy [Mandrik O, Knies S, Severens JL. Economic value of in vitro fertilization in Ukraine, Belarus, and Kazakhstan. Clinicoecon Outcomes Res. 2015;7:347-356. Published 2015 Jun 12. doi:10.2147/CEOR.S79513].

9) Methods
The outcome is clinical pregnancy. I would make this clear. But also is it clinical pregnancy per egg retrieval cycle (cumulative fresh and frozen from one egg retrieval)? How long was the followup? Did private patients do more or less embryos transfer procedure per egg retrieval compare to public patients? Please define this carefully because it makes a big difference to how the results are interpreted.

Authors' reply:

Thank you for this comment. We agree with the reviewer's standpoint that the outcome is the clinical pregnancy. The clinical pregnancy rate was calculated per egg retrieval cycle (cumulatively from fresh and frozen eggs). We found that clinical pregnancy rate per number of embryos transferred is higher in private than in public clinical settings – per egg retrieval cycle (fresh egg). This finding might be related to a lot of factors linked to physician and patient and would be analyzed as a part of PhD thesis of our candidate. Patients were followed up for three months after the last embryos transfer.

Regarding the additional question within this issue, we found that private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2, $p<0.001$), transferred more embryos (2.2±2.5 vs 1.4±1.1, $p<0.001$), and had more multiple pregnancies (0 vs 4, $p=0.32$) than the public clinics (Table 3). However, we did not collect data on how many embryos transfers were done in one

egg retrieval cycle. We added this limitation in the discussion. We could only speculate that higher pregnancy rates in private clinics could be explained by more embryos transfers done in one egg retrieval cycle to improve chances of the clinical pregnancy than in public clinics.

10) The fact that on average 2 embryos were transferred each cycle makes is hard to believe the multiple pregnancy rates of 1%, this can't be right.

Authors' reply:

Thank you for your comment. We double checked our database, analysis and interpretation and all is correct.

11) Also, is clinical pregnancy rate per number of embryos transferred the implantation rate? It was double in private clinics. Why would this be? I think this is a key finding of the paper.

Authors' reply:

The clinical pregnancy rate per embryos transferred was defined as the number of clinical pregnancies divided by number of embryos transferred. The higher pregnancy rate in the private clinics could be explained by many factors such as patient's characteristics (demographic, behavioral, etc.), high-tech equipped clinics, more experienced physicians and embryologists, difference in treatment protocol and follow-up care, and other factors. We added the following sentence in the discussion to highlight importance of this finding and how it fits to the overall discussion: "In fact, in the bivariable analysis, the clinical pregnancy rate per embryos transferred was higher in private clinics, suggesting higher-quality embryos transferred leading successful outcomes."

12) I do not think no. of oocytes is an outcome in its own right. This can be in the causal pathway and can be a direct effect of the approach to stimulation. If you consider it in the causal pathway, it arguably should not be controlled for either in your models.

Authors' reply:

We agree with the comment. It is well known that the number of oocytes retrieved is a strong predictor for the clinical pregnancy. In drawing a directed acyclic graph for the relationship between clinical settings or funding models with the clinical pregnancy, we identified that the number of oocytes retrieved was a mediator (as it stood in the unidirectional path between an exposure and the outcome). Our initial thought was to not include it in the multiple regression modeling. However, we understood if we did not adjust for it, we would not know whether observed differences between clinicals settings or funding models were solely attributed to how many oocytes retrieved or there were other indirect paths that could explain the relationship. After adjusting, we believe we underlined the existence of other factors that potentially contribute to better outcomes for private clinics (more experienced embryologists, quality embryos, and other factors) and for publicly funded women (selection of patients with better reproductive prognosis). Interestingly, we did not find any meaningful difference in the estimates of clinical settings or funding models between models with and without the number of oocytes retrieved (see STATA output below). Similarly, mediation analysis did support our conceptual understanding that the number of oocytes retrieved is the mediator variable. Thus, we decided to include it in the models so to see whether other (unfortunately, not measured) factors within clinical settings or funding models are associated with the outcome.

clinical_preg	IRR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
type_clinic						
public	.3985798	.0607983	-6.03	0.000	.2955801	.5374714
payment						
GP	1.213162	.1140588	2.06	0.040	1.008999	1.458636
age	.99587	.0072798	-0.57	0.571	.9817036	1.010241
cat_bmi						
1	.8119853	.0722945	-2.34	0.019	.681965	.9667947
2	.7219892	.1038752	-2.26	0.024	.5445844	.9571857
edu						
C	1.234603	.1598604	1.63	0.104	.95788	1.59127
D	1.391625	.1792045	2.57	0.010	1.081209	1.79116
1.comorbidity	.7762269	.0721317	-2.73	0.006	.6469786	.9312954
cat_cause_infertility						
1	.762447	.1432394	-1.44	0.149	.5275894	1.101852
2	.9586569	.0746283	-0.54	0.588	.8230003	1.116674
infertility_duration	.9996829	.0107801	-0.03	0.977	.9787759	1.021036
number_prev_trials	.9029356	.0469219	-1.96	0.049	.8154986	.9997474
number_current_embryo_t~r	1.046364	.0686105	0.69	0.489	.9201728	1.189862
_cons	.9680483	.2598217	-0.12	0.904	.5720536	1.638164

13) Results
Can you present the regression analysis in a more traditional format please showing the reference and crude and adjusted measures relative to this, so the reader can see how each variable contributed to the results.

Authors' reply:

Thank you for your comment. We added reference groups for clarity in Table 4.

14) Adding a lay interpretation of the interaction is need.

Authors' reply:

We revised and simplified the interpretation for the interaction. Please see the highlighted part in the discussion:

"Even though the relationship between clinical settings and the IVF clinical pregnancy rate was not modified by the payment type (p=0.19), we noticed that women who paid out of pocket had stronger negative association with the IVF clinical pregnancy rate (and had relatively lower number of oocytes retrieved) than patients who were publicly funded, among all women who attended public clinics."

15) I suggest asking a biostatistician to assist with the analysis and presentation. The general methods are appropriate but advice on the model specification and presentation are needed.

Authors' reply:

Thank you for your comment. We added reference groups for clarity in Table 4. Additionally, we created Table 5 to simplify presentation of the effect modification of funding model on the relationship between clinical settings and number oocytes retrieved and IVF clinical pregnancy. See Tables 4 and 5.

16) Discussion

There appear to still be contradictions the role that prognosis of the patients play. It appears from the text that public funding is made available to those with a good prognosis, but then it is said that private clinics choose good prognosis patients. Can you please make this clear?

Authors' reply:

Interestingly, the government funding is not designated only to the public sector, but also on competitive basis provided for patients seeking care at private clinics. In order to implement competitive and business environment in the health care the government proposed a system where "The money follows the patient". At the same time, public clinics are not confined and can provide out-of-pocket services as well. So, here we are looking in a very peculiar relationship between clinical settings and funding models in terms the IVF outcomes. Public funding does not mean that purely the public sector is involved in providing care. Similarly, we self-paid patients are not necessary all seek care in the private sector.

To highlight this point, we added the following statement in the discussion: "Since government funded IVF cycles can be performed in both clinical settings as the government encourages the private sector to provide health care services under the governmental support and similarly the public sector is stimulated to provide services on self-paid basis, it was of the study interest to investigate the interaction between clinical settings and funding type in predicting the IVF outcome."

In a simplistic way to unveil this complex relationship, we stratified the distribution of the clinical outcomes between the clinical settings by the funding models (see contingency tables below):

Government funded

	Clinical pregnancy, n(%)		
Clinical setting	no	yes	Total
private	1 (4.0)	26 (96.0)	27 (100)
public	44 (63.8)	25 (36.2)	69 (100)
Total	45 (46.9)	51 (53.1)	96 (100)

Self-paid

	Clinical pregnancy, n(%)		
Clinical setting	no	yes	Total
private	39 (22.3)	136 (77.7)	175 (100)
public	39 (79.6)	10 (20.4)	49 (100)
Total	78 (34.8)	146 (65.2)	224 (100)

In the contingency tables, we overall observed that independent of the funding models private clinics had greater clinical pregnancy rates than public ones. Also, what we noticed that government supported women had higher clinical pregnancy rates regardless of the clinical settings than self-paid ones.

17) There is a lot and of missing data and we have no way of knowing whether this is truly missing at random – only that equal proportions were missing from public and private clinics. Thus don't agree with your point on page 13.

Authors' reply:

Thank you for this comment. It is true that we do not know whether non-respondents were missing at random or not. We proposed that if the non-response rates were similar in both clinical settings then it should not attenuate (conceptually) the association between the clinical setting and the IVF outcomes. However, this statement does not have any theoretical or real data evidence. We do not have demographic, clinical and follow-up data of non-respondents. Thus, we decided to remove it from the text.

18) It would be very nice to see this paper published and I encourage the authors to keep working on it, but the analysis needs to be correct, limitations made clear, and conclusions only reflect results.

Authors' reply:

Thank you for your encouragement. We tried to address all your comments and hope you will find the updated revision more suitable for publication.

VERSION 3 – REVIEW

REVIEWER	Bahadur, Gulam North Middlesex University Hospital, Reproductive Medicine Unit
REVIEW RETURNED	16-Aug-2021

GENERAL COMMENTS	The objective needs to be stated clearly and be asking a question Conclusion needs to be balances The limitations need to be made clear and simple RE-referee "Impact of governmental support to the IVF outcome: differences between public and private clinical settings. A prospective cohort study." There is considerable improvement but equally some of the messages are being lost though over explanation in responses to referees and where some contradictions appear to arise. Relying on researchgate reports and obscure references do not help either. I accept it is a prospective study. However, it is equally worrying to select out data based on criticism or not liking data. [To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis]. They do reveal the level of selection bias which could explain some of the results of their study. The high demand for IVF treatment through public funding in Kazakhstan while women with

	better prognosis are usually selected – “skimming the cream off the milk”. Private clinics had a substantially higher (this should be altered to significant) clinical pregnancy rate but private clinics had a lower percentage of overweight or obese women and a lower proportion of women with comorbidities than public clinics. This needs to form a substantial part of the conclusion statement. They also explain, `On the other hand, private clinics try to select also patients with better prognosis or transfer more than one embryo so to increase chances of pregnancy’. If the latter is true this will mean multiple births will increase beyond the 10% level seen for example in the UK and many Western countries despite having eSET policies. The level of multiple births could be explained if fetal reduction is taking place but success in IVF is live birth against low multiple births rates. Clinical pregnancies are fraught with interpretation and follow up problems. Private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2 ….and had more multiple pregnancies (0 vs 4, p=0.32) than the public clinics. The other common theme running is to explain away better outcomes for private clinics being due more experienced embryologists, quality embryos, and other factors, while for publicly funded women (selection of patients with better reproductive prognosis). There is no evidence whatsoever but by repeating these almost become self-prophesising that these are the reasons which makes success. At another point in the explanation, publicly funded women with difficult prognosis had no choice but be treated there. They need to make the manuscript free flowing and where there is no evidence they state the status quo and refrain from adding more comments. They stated `due to COVID-19, it was not possible (and still it is challenging) to access patient follow-up data for 22% of the participants. We acknowledged this weakness in the discussion section’ However in their explanation they follow up 3months after the embryo transfer. Women in the study group had been attending ART clinics between June 2019 and September 2020 and I would expect to see a more robust set of data by June 2021 when they submitted the manuscript? Their conclusion Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. The difference in IVF pregnancy rates and MULTIPLE GESTATION PREGNANCY between private and public clinics is not only associated with demographical and clinical characteristics of patients ~~but also could be related to factors associated with the clinical settings~~. There is also a need to further investigate whether the increase in

	public funding would influence clinical pregnancy rates and ~~potentially live birth rates~~ among subfertile women *but also could be related to factors associated with the clinical settings*- this **needs to be dropped** as there is an attempt to promote a variety of marketing elements which are not substantiated. *potentially live birth rates*- **drop this** as they cannot be talking about live birth when the main weakness is the inability to tell us what the Live birth rate was Introduce multiple births into the conclusion I am certain further improvements and clarification can be made. I feel overall they are nearly there but need to mellow some of the claims while improving the manuscript further.

VERSION 3 – AUTHOR RESPONSE

Reviewer #1 comments:

1) The objective needs to be stated clearly and be asking a question

Authors' reply:

We thank the Reviewer for the valuable comment. We rephrased the research questions and made them actual questions.

2) Conclusion needs to be balances

Authors' reply:

We revised the conclusions section. Please see the highlighted text in the manuscript.

3) The limitations need to be made clear and simple

Authors' reply:

The strengths and limitations section was revised. Please see the main text.

Reviewer #2 comments:

4) There is considerable improvement but equally some of the messages are being lost though over explanation in responses to referees and where some contradictions appear to arise. Relying on researchgate reports and obscure references do not help either.

Authors' reply:

We performed thorough literature search and found only a couple of publications describing women attending IVF clinics in Kazakhstan. Both are open access publications available in Google Scholar.

- *Reference #14 "Lokshin VN, Khoroshilova IG, Kuandykov EU. Personified approach to genetic screening of infertility couples in ART programs. Report of the national academy of sciences of the republic of Kazakhstan. 2018; 1(317): 37–41. ISSN 2224-5227"*
- *V.N.Lokshin, M.D. Omar, Sh.K. Karibaeva, T.M. Dzhusubalieva, S.B. Baikoshkarova, A.A. Akhmetova, L.I. Pokotilo, K.S. Dyusembinov, S.S Tararaka, N.S. Tararaka. Assisted reproductive technologies in Kazakhstan in 2017: Summary report on efficiency and availability. Public Health, 2020; 3 (44):8-14. https://doi.org/10.37800/RM2020-1-19.*

Since, there are not a lot of information published on this field from Kazakhstan, we had to rely on the available data.

5) I accept it is a prospective study. However, it is equally worrying to select out data based on criticism or not liking data. [To minimize selection bias in the results, 108 patients from one private clinic with the extremely high pregnancy rate (98.1%) were excluded from the further analysis]

Authors' reply:

Regarding 108 patients, they were not excluded from the main analysis. The results were obtained from the whole complete case analytical dataset (n=347). However, we were concerned about high pregnancy rate in one clinic which could be associated with selection bias, thus we decided further perform sensitivity analysis with the analytical dataset excluding those 108 patients. The results from both analyses were consistent indicating robustness of the findings.

6) They do reveal the level of selection bias which could explain some of the results of their study. The high demand for IVF treatment through public funding in Kazakhstan while women with better prognosis are usually selected – "skimming the cream off the milk". Private clinics had a substantially higher (this should be altered to significant) clinical pregnancy rate but private clinics had a lower percentage of overweight or obese women and a lower proportion of women with comorbidities than public clinics. This needs to form a substantial part of the conclusion statement.

Authors' reply:

We appreciate the comment. We added these findings in the conclusion.

7) They also explain, `On the other hand, private clinics try to select also patients with better prognosis or transfer more than one embryo so to increase chances of pregnancy'. If the latter is true this will mean multiple births will increase beyond the 10% level seen for example in the UK and many Western countries despite having eSET policies. The level of multiple births could be explained if fetal reduction is taking place but success in IVF is live birth against low multiple births rates. Clinical pregnancies are fraught with interpretation and follow up problems.

Authors' reply:

We really appreciate this comment and agree with the reviewer. In the UK and many Western countries transfer of more than one embryo increases the chances of multiple pregnancy (despite having elective

single embryo transfer policy). We agree with the standpoint that success in IVF means the live birth against low multiple birth rates. In our study private clinics retrieved higher number of oocytes, transferred more embryos and had more multiple pregnancies than public clinics, as presented on Table 3. As this was an observational study with a small sample size, we were not able to estimate the "true" multiple pregnancy rate in Kazakhstan. But what we observed is that only 4 patients had twin pregnancies in private clinical settings, and embryo reduction procedures were not performed. It would be interesting further investigate whether multiple pregnancies are likely seen only private settings, and whether the multiple gestation pregnancy rate is higher than 10% in Kazakhstan.

8) Private clinics retrieved, on average, higher number of oocytes (11.5±8.4 vs 8.1±7.2 ….and had more multiple pregnancies (0 vs 4, p=0.32) than the public clinics.

Authors' reply:

We incorporated this finding into the conclusion.

9) The other common theme running is to explain away better outcomes for private clinics being due more experienced embryologists, quality embryos, and other factors, while for publicly funded women (selection of patients with better reproductive prognosis). There is no evidence whatsoever but by repeating these almost become self-prophesising that these are the reasons which makes success. At another point in the explanation, publicly funded women with difficult prognosis had no choice but be treated there. They need to make the manuscript free flowing and where there is no evidence they state the status quo and refrain from adding more comments.

Authors' reply:

We thank the Reviewer for this valuable comment. We agree that some of the unsupported explanations could be misleading. So, we removed some of the unsupported speculations, particularly, the speculative discussions about private clinics having more experienced embryologists, quality embryos, and other factors based on the bivariate analysis in the discussion section. Please see the highlighted text in the manuscript.

10) They stated `due to COVID-19, it was not possible (and still it is challenging) to access patient followup data for 22% of the participants. We acknowledged this weakness in the discussion section' However in their explanation they follow up 3months after the embryo transfer. Women in the study group had been attending ART clinics between June 2019 and September 2020 and I would expect to see a more robust set of data by June 2021 when they submitted the manuscript?

Authors' reply:

COVID-19 has been influencing our clinical work and overall daily life, starting from the spring 2020. As written in "Methods" section, our study involved patients from June 2019 to September 2020. Due to COVID pandemic (unfortunately still existing), we were not able to follow up 22% of patients 3 months after embryo transfer (they were lost to follow-up). As study was terminated in 2020, we don't have data by June 2021, as asked by the reviewer. While we presented incomplete data (n=446) with missing values in descriptive tables (Table 1, 2 and 3), we performed the main analysis using the complete case analytic dataset (n=347).

11) Private clinics and public funding were independently associated with higher IVF clinical pregnancy rates. The difference in IVF pregnancy rates and MULTIPLE GESTATION

PREGNANCY between private and public clinics is not only associated with demographical and clinical characteristics of patients ~~but also could be related to factors associated with the clinical settings~~. There is also a need to further investigate whether the increase in public funding would influence clinical pregnancy rates and ~~potentially live birth rates~~ among subfertile women.

but also could be related to factors associated with the clinical settings- **this needs to be dropped** as there is an attempt to promote a variety of marketing elements which are not substantiated.
potentially live birth rates- **drop this** as they cannot be talking about live birth when the main weakness is the inability to tell us what the Live birth rate was

Authors' reply:

We agree with the comment and suggestions. We altered the conclusions section accordingly to highlight the main findings of the study (please see the highlighted text in the manuscript).

12) Introduce multiple births into the conclusion

Authors' reply:

We thank the Reviewer. We added multiple pregnancies in the conclusion.

13) I am certain further improvements and clarification can be made. I feel overall they are nearly there but need to mellow some of the claims while improving the manuscript further.

Authors' reply:

We greatly appreciate the Reviewers' comments and time spent reviewing our manuscript. Based on your comments, we feel that the manuscript considerably improved.