

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20183308>

Original Research Article

Luteal phase serum progesterone level as a predictor of vaginal bleeding or adverse pregnancy outcome in patients undergoing assisted reproductive techniques

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Received: 16 May 2018

Accepted: 23 June 2018

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ABSTRACT

Background: With advances in assisted reproductive techniques its becoming increasingly important to identify pregnancies having a potential of adverse outcome in the form of per vaginal bleeding or early pregnancy loss. The objective of this study was to find out whether the value of luteal phase progesterone can be used as a marker to predict the possibility of per vaginal bleeding and early pregnancy loss in cases conceived by in vitro fertilization (IVF) and embryo transfer (ET).

Methods: A total of 40 women of age less than or equal to 40 years undergoing IVF and ET were included in this study depending upon inclusion criteria. Patients were excluded if they had any factor defined as exclusion criteria. on D14 after embryo transfer B-hCG was done in all the patients. If B-hCG levels were found to be ≥ 100 mIU/ml then serum progesterone levels were also done. B-hCG levels were repeated after 48 hours. Pregnancies were followed up and correlation between suboptimal rise in serum progesterone levels and adverse pregnancy outcome was studied.

Results: Mean Beta-hCG and Serum progesterone levels on D14 of embryo transfer were found to be 388.86 ± 34 mIU/ml and 54.24 ± 4.32 ng/ml respectively. A repeat B-hCG and serum progesterone level 48 hours after initial estimation showed mean B-hCG and serum progesterone level to be 598.80 ± 52.12 mIU/ml and 72.24 ± 5.24 ng/ml respectively. Out of 40 patients 26 patients showed $>30\%$ rise in serum progesterone level while 14 patients showed less than 30% rise in serum progesterone level.

Conclusions: Suboptimal rise in serum progesterone level ($<30\%$) was associated with increased incidence of adverse pregnancy outcome in women conceived after in vitro fertilization and embryo transfer.

Keywords: Adverse pregnancy outcome, B-hCG, Embryonal transfer, In vitro Fertilization, Luteal phase progesterone levels

INTRODUCTION

The incidence of infertility is increasing in modern developed world. It affects approximately 15-20% of the population with some geographic and demographic variations. In developing world, the common causes of infertility may include tuberculosis, pelvic inflammatory diseases, maternal chromosomal anomalies, Mullerian anomalies in females.¹ Male factors responsible for

infertility may include varicocele, azoospermia, substance abuse, congenital bilateral absence of vas deferens (CBAVD) and post chemo or radiotherapy. In developed world women delay their first pregnancy for various reasons including ambitions and work pressure which may lead to increased difficulty to conceive at an advanced age. In many instances the exact cause of infertility cannot be made out and this then is labelled as infertility due to unexplained reasons.²

While in some instances the infertility can be dealt with by specific treatment like antitubercular drugs for tuberculosis, surgery for varicocele and surgical interventions in cases of tubal blockade due to pelvic inflammatory disease etc. There are instances when it's impossible for a woman to conceive without assisted reproductive techniques.³ Such instances include azoospermia, congenital absence of vas deference or seminal vesicles amongst others. In all such instances assisted reproductive techniques like In vitro fertilization (IVF), Gamete intrafallopian transfer (GIFT), Zygote intrafallopian transfer (ZIFT), Intracytoplasmic sperm injection (ICSI), In vitro fertilization (IVF), Gamete intrafallopian transfer (GIFT), Zygote intrafallopian transfer (ZIFT), Intracytoplasmic sperm injection (ICSI) becomes essential.⁴

With advances in assisted reproductive techniques and increasing acceptance of these techniques by the society at large there is a tremendous increase in the number of the couples going for assisted reproductive techniques. With increase in conceptions following these techniques there is also an increased in the number of complications seen in patients who have conceived after these techniques.⁵

It's a well-known fact that the pregnancies after assisted reproductive techniques are associated with an increased risk of complications, for example ectopic pregnancies, as compared to natural conceptions. These pregnancies are also associated with considerable amount of anxiety about the outcome on the part of prospective parents as well as concerned obstetrician. Therefore, it's important to reliably predict the possibility of adverse outcome in these pregnancies.⁶ Serum Progesterone and serum B-hCG levels have been of immense interest for researches to predict the outcome of conceptions after ART.⁷

Serum progesterone is crucial for bringing about the endometrial changes that are essential for implantation and successful continuation of the pregnancy. It is found to have a complex role in maintaining pregnancy by its effect on T-helper cells.⁸

It moreover is responsible for synthesizing various anti-abortion factors including nitrous oxide production (thereby increasing blood and oxygen supply to endometrium) and progesterone-induced blocking factor.⁹ Given its anti-abortion effects it has been the subject of various studies and many researches have studied the effect of progesterone levels on the outcome of pregnancies. This becomes all the more important in cases of conceptions after ART.¹⁰

We conducted this prospective study of 40 women who had undergone ART and ET to find out whether luteal phase progesterone levels can be used as a marker to predict the possibility of Per vaginal bleeding and early pregnancy loss.

METHODS

This was a prospective cohort study of 40 patients who had undergone ART and ET to find out whether luteal phase progesterone levels can be used as a marker to predict the possibility of per vaginal bleeding and early pregnancy loss. The study was conducted in ART Centre of a tertiary care hospital situated in an urban area. The informed consent was obtained from all the patients before enrolling them in the study. The patients were included in this study on the basis of a predefined inclusion criteria. Any patient having any exclusion criteria was excluded from the study.

Detailed history and demographic profile was noted in all the patients. on D14 after embryo transfer B-hCG was done in all the patients. If serum B-hCG levels were found to be 100 ng/ml or above then serum progesterone levels were also done. B-HCG levels were repeated after 48 hours. Cases with less than 60% increase in BHCG levels from previous levels were excluded from the study. In remaining patients repeat serum progesterone levels were also repeated. A minimum rise of 30% from the previous level was taken as the cut-off value and the patients were divided on the basis of whether rise of serum progesterone level was more or less than 30% of previous value. The incidence of vaginal bleeding and adverse pregnancy outcome was studied in the studied cases. variables were analyzed using paired' test. For statistical comparisons P value less than 0.05 was taken as significant. Results were tabulated and analyzed using SPSS 16.0 version software. Microsoft word and excel were used for generating charts and graphs.

Inclusion criteria

- All the patients who had undergone ICSI and embryo transfer for infertility
- Age of the patients less than 40 years
- Patients who have given informed consent.

Exclusion criteria

- Age more than 40 years
- Those who refused consent to be part of the study.

RESULTS

Out of the 40 studied cases 24 (60%) patients had minimum rise serum progesterone by 30% (Group A) while 16 (40%) patients had risen of less than 30% (Group B) from the previous level.

Table 1: Comparison of the mean age of the studied cases.

	Mean age of the studied cases	P value
Group A	31.64±3.12	0.16
Group B	34.24±3.38	Not significant

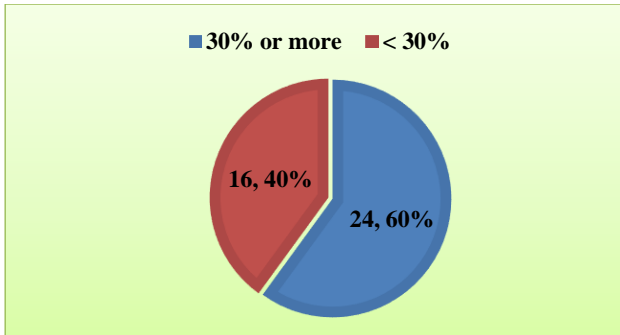


Figure 1: Rise of Serum progesterone level in studied cases.

The analysis of age of the patients belonging to both the groups showed that the mean age of patients in Group A was found to be 31.64 ± 3.12 years while in group B the mean age was found to be 34.24 ± 3.38 years. The mean

age in both the groups was found to be comparable and there was no statistically significant difference in mean age.

Table 2: Comparison of the body mass index in the studied cases.

	Mean BMI of the studied cases	P value
Group A	26.12 ± 3.98	0.78
Group B	25.78 ± 3.76	Not significant

The analysis of Body mass index of the studied cases showed that the mean BMI of group A was 26.12 ± 3.98 while mean BMI of group B was found to be 25.78 ± 3.76 . The mean BMI of both the groups were found to be comparable and there was no statistically significant difference in BMIs of both the groups.

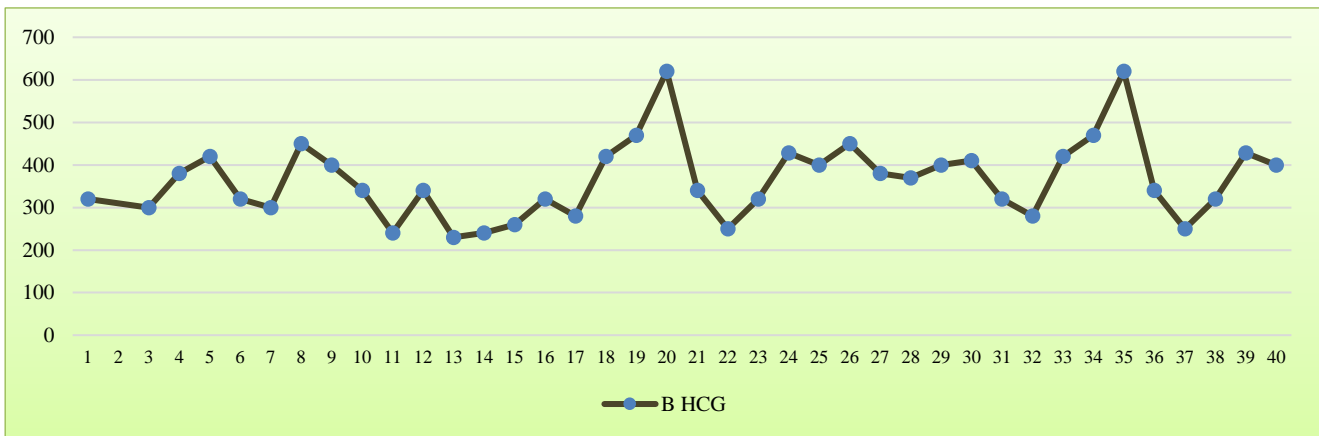


Figure 2: Luteal Phase B-hCG levels in the studied cases.

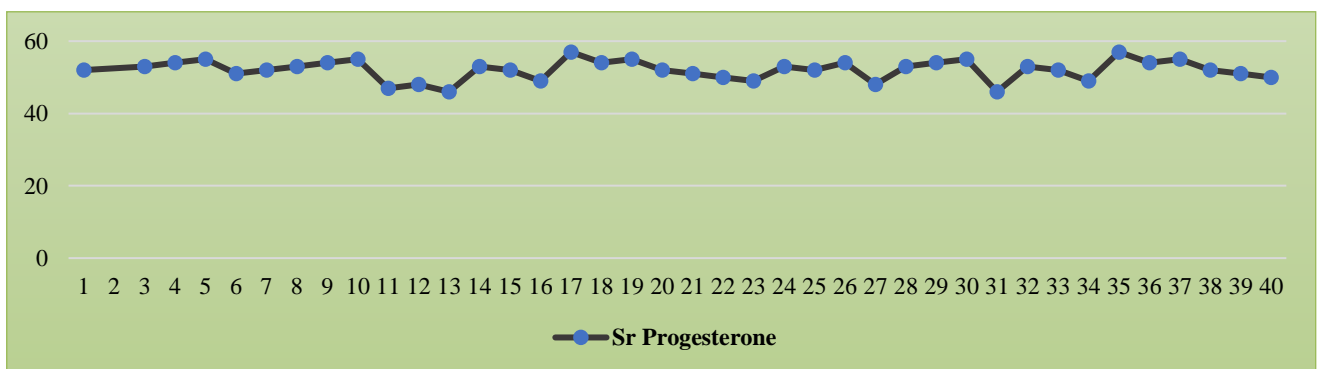


Figure 3: Luteal phase serum progesterone levels in the studied cases.

In both the groups B-hCG was done on D14 after embryo transfer in all the patients. If B-hCG levels were found to be 100 mIU/ml or more then serum progesterone levels were also done. The Mean B-HCG level was found to be 388.86 ± 34 mIU/ml in the studied cases.

Similarly, Serum progesterone were also done on D14 provided that the BHCG level in these patients were found to be more than 100 mIU/ml. The mean progesterone levels were found to be 54.24 ± 4.32 ng/ml.

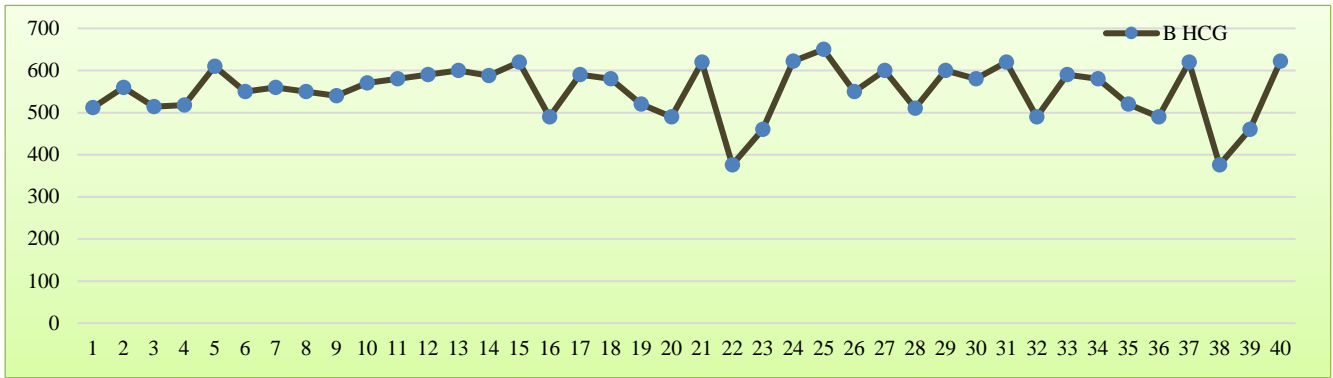


Figure 4: B-hCG levels after 48 hours (D 16) in the studied cases.

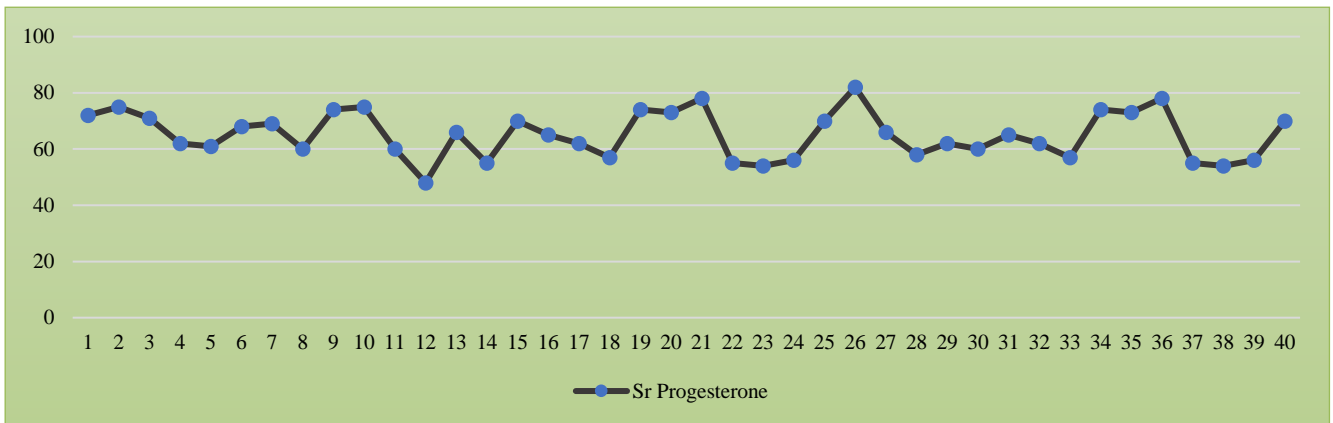


Figure 5: Serum progesterone levels after 48 hours (D 16) in the studied cases.

B HCG and serum progesterone levels were repeated after 48 hours (on D16). The Mean B-HCG level was found to be 598.80 ± 52.12 mIU/ml. The patients in whom there was less than 60% increase in B-HCG level were excluded from further study.

The Mean Sr Progesterone levels was found to be 72.24 ± 5.24 ng/ml. The patients were divided on the basis of whether there was more than 30% increase in serum progesterone levels as compared to previous reading.

Table 3: Comparison of Mean B-hCG and serum progesterone levels on D14 and 48 hours later.

	On D14 of embryo transfer	48 hours after initial readings
Mean B-hCG	388.86 ± 34 mIU/ml	598.80 ± 52.12 mIU/ml
Mean Sr Progesterone	54.24 ± 4.32 ng/ml.	72.24 ± 5.24 ng/ml

Out of the studied cases 24 patients had more than 30% increase in serum progesterone levels (Group A) while 14 patients showed less than 30% rise in the levels of serum

progesterone levels as compared to previous reading (Group B).

The comparison of mean BHCG and Sr Progesterone showed that on D14 mean BHCG and Sr Progesterone were 388.86 ± 34 mIU/ml and 54.24 ± 4.32 ng/ml respectively while repeat levels after 48 hours showed that them to be 598.80 ± 52.12 mIU/ml and 72.24 ± 5.24 ng/ml respectively.

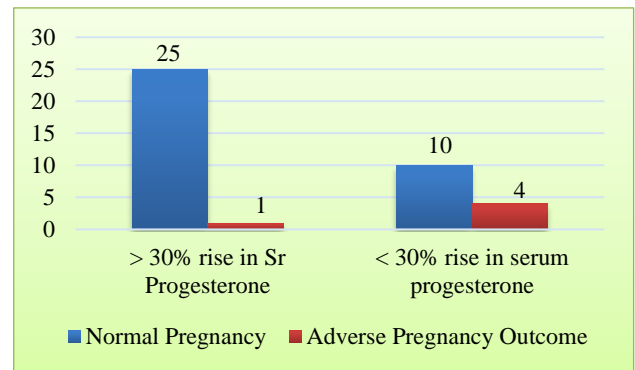


Figure 6: Comparison of rise in serum progesterone level and pregnancy outcome.

The patients were followed up further to find out whether there was any relation between suboptimal rise in progesterone levels and pregnancy outcome. Out of 26 patients who had more than 30% rise in serum progesterone levels only 1 patient had episode of vaginal bleeding or abortion. While out of 14 cases in whom there was less than 30% rise in serum progesterone levels 4 patients either had episodes of vaginal bleeding or adverse pregnancy outcome in the form of abortion.

Table 4: Comparison of rise in mean serum progesterone levels and pregnancy outcome.

	Normal Pregnancy	Bleeding PV or adverse pregnancy outcome	Total
> 30% rise in Sr Progesterone	25	1	26
Suboptimal rise in Sr Progesterone (<30%)	10	4	14
Total	35	5	40

Fishers Extract Test P= 0.0426 (Statistically significant)

The suboptimal rise in serum progesterone levels (< 30%) was associated with increased chances of either vaginal bleeding or adverse pregnancy outcome in the form of abortion. The chances of these events were relatively less in patients in whom there was rise of serum progesterone level by more than 30% of the baseline levels done on D14. The fisher's extract test showed p value to be 0.042 and hence the difference was found to be statistically significant (P = 0.0426).

DISCUSSION

Assisted reproductive techniques are becoming increasing acceptable in modern society. With this acceptance naturally comes the increased incidence of complications following these techniques. pregnancy after assisted reproductive techniques are associated with increased chances of complications and adverse pregnancy outcomes and are more likely to be associated with immense mental trauma to the prospective parents.¹¹ It is therefore important to reliably predict the possible outcome of the pregnancy. B HCG level estimation is one of the important step in finding out whether the pregnancy is viable and progressing normally. Adequate progesterone secretion in the luteal phase of in vitro fertilization and embryo transfer cycles is one of the most important factors responsible for proper implantation and pregnancy sustenance.¹² There are many studies undertaken by various researchers to know whether luteal phase serum progesterone level could be used to predict the pregnancy outcome in patients who have conceived after ART particularly in vitro fertilization and embryo transfer.¹³

Guth B et al in their study of 111 patient undergoing in vitro fertilization (IVF) and embryo transfer found that out of these 111 patients 80.2%, had ongoing pregnancies. Moreover, the authors found that If the level was less than 300, the ongoing multiple pregnancy rate was 9% (5/57). If the level was between 300 and 600, the ongoing pregnancy rate was 40% (10/25). If the hCG level was greater than 600, the multiple pregnancy rate was 100% (7/7).¹⁴ Similar findings were reported by other authors like Slattengren AH et al and Jie Z et al.^{15,16}

The value of B HCG alone in predicting multiple pregnancy and pregnancy wastage in an in vitro ET fertilization cycle has been subject of many studies with conflicting outcome. Singh N et al conducted a study assess the prognostic value of serum beta human chorionic gonadotropin (β hCG), measured on day 14 post embryo transfer (ET) for predicting multiple gestation and pregnancy wastage in women undergoing in vitro fertilization ET (IVF-ET). Out of the 168 patients who conceived after IVF treatment, 114 (68%) were viable pregnancies (delivered/ongoing). Among the viable pregnancies, 97 (85%) had a successful pregnancy outcome and the remaining 17 patients are ongoing pregnancies. Median values of β hCG (625 IU/L) among viable pregnancies was significantly (P < 0.05) higher than that of nonviable pregnancies (174 IU/L). The authors concluded that β hCG cutoff values determined on day 14 post ET by ROC curve analysis are useful in discriminating between multiple pregnancy and pregnancy losses. The authors recommended that these cutoff values might aid in the prognosis, clinical management, and counseling of the IVF patients.¹⁷

Kaur J et al conducted a prospective study of 145 women undergoing embryo transfer (ET) to find out whether mid-luteal serum progesterone (P) levels' impact pregnancy outcome in fresh and frozen embryo transfer (FET) cycles. In this study Serum progesterone levels were assessed for all the patients in the mid-luteal phase. Patients were divided into groups based on the type of ET performed. These groups were further subdivided based on mid-luteal serum P levels being below (Groups A1/B1) or above 15 ng/mL (Groups A2/B2). Progesterone levels were correlated with the clinical pregnancy outcome. The authors found that Patients with mid-luteal serum P levels <15 ng/mL (Group A1) in fresh ET cycles had a statistically significant lower clinical pregnancy rate (CPR) (P = 0.049). In FET cycles, though there was no difference in the CPR, the percentage of biochemical pregnancies was significantly higher in the group with P levels <15 ng/mL (Group B1) (P = 0.024). The study found that mid-luteal serum P levels <15 ng/mL have a negative impact on pregnancy outcome in both fresh (<CPR) and FET (>biochemical pregnancies) cycles. The authors concluded that Individualizing luteal phase support by measuring serum progesterone levels might help to enhance pregnancy outcomes in patients undergoing ART.¹⁸

Kim YJ et al conducted a prospective study of 148 women with visible gestational sac after IVF to evaluate the predictive value of the progesterone level at the beta-human chorionic gonadotropin (β -hCG) check day for ongoing pregnancy maintenance in in vitro fertilization (IVF) cycles in women with previous unexplained repeated miscarriages. The authors found that β -hCG >126.5 mIU/mL and progesterone >25.2 ng/mL showed higher ongoing pregnancy rates [98.0% (49/50) versus 41.8% (41/98)] than those with β -hCG \leq 126.5 mIU/mL or progesterone \leq 25.2 ng/mL. On the basis of these findings the authors concluded that the progesterone level at 14 days after oocyte retrieval can be a good predictive marker for ongoing pregnancy maintenance in women with repeated IVF failure with miscarriage, together with the β -hCG level. The combined cut-off value of progesterone >25.2 ng/mL and β -hCG >126.5 mIU/mL may suggest a good prognosis.¹⁹ Similar findings were seen in studies conducted by Abdelazim IA et al.²⁰

CONCLUSION

In women who had conceived after In vitro fertilization and embryo transfer B-hCG and Serum progesterone levels done on D14 and repeated after 48 hours may be used as a reliable predictor of adverse pregnancy outcome. Suboptimal rise in serum progesterone level (< 30%) is associated with increased incidence of adverse pregnancy outcome. Prospective parents can be appropriately counselled about possibility of adverse pregnancy outcome if such a suboptimal rise in serum progesterone is noted.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Kale A, Kale A. Fetal Doppler for prediction of adverse perinatal outcome in preeclampsia in a low resource setting. *Int J Reprod Contracept Obstet Gynecol* 2018;7:3152-7.