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Original Article: Obstetrics

A Randomized Double Blind Placebo controlled trial to evaluate the Role of Antioxidants (Vitamin C & Vitamin E) in Prevention of Pre-Eclampsia

Prof. (Dr.) Picklu Chaudhuri,[1] Dr. Mukul Ranjan Barik[2]

Abstract

Aim: The study aimed to evaluate the role of antioxidants (Vitamin C & Vitamin E) supplementation from early mid-trimester till delivery in prevention of pre-eclampsia.

Method: In a randomized double-blind placebo controlled trial conducted in the Dept. of Gynaecology and Obstetrics, N.R.S Medical College & Hospital, Kolkata, women attending antenatal OPD in second trimester,after screening for eligibility and giving consent, were randomized to receive either 1000 mg Vitamin C tablet once daily and 400 mg Vitamin E capsule once daily starting from 12 weeks to 19 weeks 6 days or matched placebo till delivery ; Both the categories were observed throughout the antenatal period till up to one week of post-partum period. Primary outcome measure was incidence of Gestational hypertension, Pre-eclampsia and Eclampsia and secondary outcome measures were adverse feto maternal outcome.

Result: Total 276 women (92 in high risk & 184 in low risk group), were randomized Overall incidence of hypertensive disorders of pregnancy was slightly lower in vitamin supplemented than non-supplemented groups irrespective of risk factors, the differences, however failed to reach statistical significance (high risk: p=0.35, RR 0.67, 95% CI 0.34-1.33 & in low risk: p=0.36, RR 0.69, 95% CI 0.34-1.40).

Conclusion: Antioxidants (Vitamin C and Vitamin E) supplementation in pregnancy did not cause significant reduction of incidence of pre-eclampsia and other hypertensive disorders of pregnancy, as well as it did not alter other maternal and fetal outcomes in women with or without risk factors.

Keywords: Antioxidants, Vitamin C, Vitamin E, Pre-Eclampsia.

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Introduction

Pre-eclampsia, affecting 3-10 % of all pregnancies, is one of the most important cause of maternal and perinatal morbidity and mortality.[1] Pre-eclampsia can affect the kidney, liver, brain and the blood clotting system and thus causes potentially life threatening complications of mother. Also the condition is associated with poor fetal growth, prematurity and related fetal morbidity and mortality.[2]

Although several hypotheses have been proposed, the causes of preeclampsia remain unclear. Oxidative stress of the placenta is considered to be a key intermediary step in the pathogenesis of preeclampsia. This hypothesis is supported by strong evidence of increased concentrations of biomarkers for oxidative stress and decreased concentrations of antioxidants such as vitamins C and E in the serum and tissues of women with established preeclampsia compared to those without this disorder.[3] Oxidative stress arises from increased production of reactive oxygen species (ROS) or deficiency in antioxidant nutrients. The placenta, maternal leukocytes, and the maternal endothelium are likely contributors for free radical generation in preeclampsia which can result in the platelet aggregation and vasospasm, the two important characteristics of preeclampsia, by inactivating endothelium-derived relaxing factor, and inhibiting prostacyclin synthesis.[4,5]

Antioxidants are important in maintaining cellular function in normal pregnancy and act through inhibition of peroxidation, thus protecting enzymes and proteins as well as cell integrity. Vitamins C and E are antioxidants: vitamin C scavenges free radicals in the aqueous phase, whereas vitamin E acts in vivo to prevent lipid peroxidation, protecting against oxidative stress-related damage of cellular and intracellular structures. Vitamin C and E also maintain the vasodilator status of blood vessels by inhibiting the formation of free radicals by oxidation of nitric oxide (NO), the most important endothelium-dependent vasodilator, which is highly susceptible to oxidative damage.[6] Synergism between the actions of vitamin E and vitaminC is also reported[7] These observations led to the hypothesis that early supplementation with antioxidants could be effective in decreasing oxidative stress and improving vascular endothelial function, thereby preventing or ameliorating the course of preeclampsia.

In spite of strong theoretical background, majority of trials and meta-analysis of randomized clinical trials of antioxidants supplementation failed to document any benefits in prevention of preeclampsia.[8–13] However, the related trials India where incidence of preeclampsia is high and where poor nutrition is common, is lacking. Therefore, research needed to continue to find out whether early supplementation of antioxidants (combined vitamin C & vitamin E) prevent or modify the onset and severity of pre-eclampsia in this part of the world.

Our study was designed to test the hypothesis that supplementation of pregnant women with antioxidants would alter endothelial cell injury linked to preeclampsia reducing the incidence of hypertensive disorder during pregnancy in woman at high risk and low risk for the disorder.

Method

The study was conducted in the Department of Gynaecology and Obstetrics, Nilratan Sircar Medical College & Hospital, Kolkata during May 2014 - April 2015. The study included pregnant women, aged 15-40 years, with gestational age between 12 weeks to 19 weeks 6 days. Women were excluded if they had known medical disorders like diabetes, chronic renal disease, heart disease, thyrotoxicosis, connective tissue disorders, pheochromocytoma, severe anaemia or other haematological disorder, Known placental abnormalities, molar pregnancy, major fetal anomaly and if they were not willing to participate. The protocol was approved by the Institutional Ethical Committee. All Women attending the antenatal clinic during 12 weeks to 19 weeeks 6 days of gestation were interviewed and examined to screen for eligibility. Those who fulfilled the eligibility criteria were given informed written consent. Eligble and consenting women were now stratified into high risk and low risk categories for development of Preeclampsia. They were considered high risk if they were elderly (>35yrs), teenager,had previous history of preeclampsia, history of chronic hypertension, obese (BMI ≥30) and past history of polycystic ovarian disease.Each strata were separately randomized using computer generated random numbers sequence and serially numbered opaque sealed envelopes to assign the groups. Women assigned to study group were given packets containing vitamin C 1000 mg in tablet form and Vitamin E

400 mg in capsule form, both to be taken once daily. Women assigned to control group were given placebo tablet and empty capsule of similar size and shape and colour as the Vitamins. Treatment was started for both groups between 12 weeks to 19 weeks 6 days and foils were checked at each visit to ensure regular intake.

Group allocation and distribution of medicine packets were done by residents not involved with the trial. The investigator (outcome assessor) and participants were blinded to group assignment.

Women were followed throughout the antenatal period till one week of delivery. During each visit weight & blood pressure were measured, routine obstetric examination was done. Urine for protein by dip stick was done in each visit along with other routine investigations. Hospitalization was done if BP was 140/90 or more and investigations as platelet count, LFT (Transaminases) LDH, urea-creatinine, uric acid and 24 hour urine protein were performed. Coagulation profile was measured in severe cases.Investigation were repeated weekly or earlier according to individual need. Women were followed up till delivery and antenatal complication, if any,were recorded. Gestational age at delivery, mode of delivery, any complication during labour and one week postpartum were also recorded.

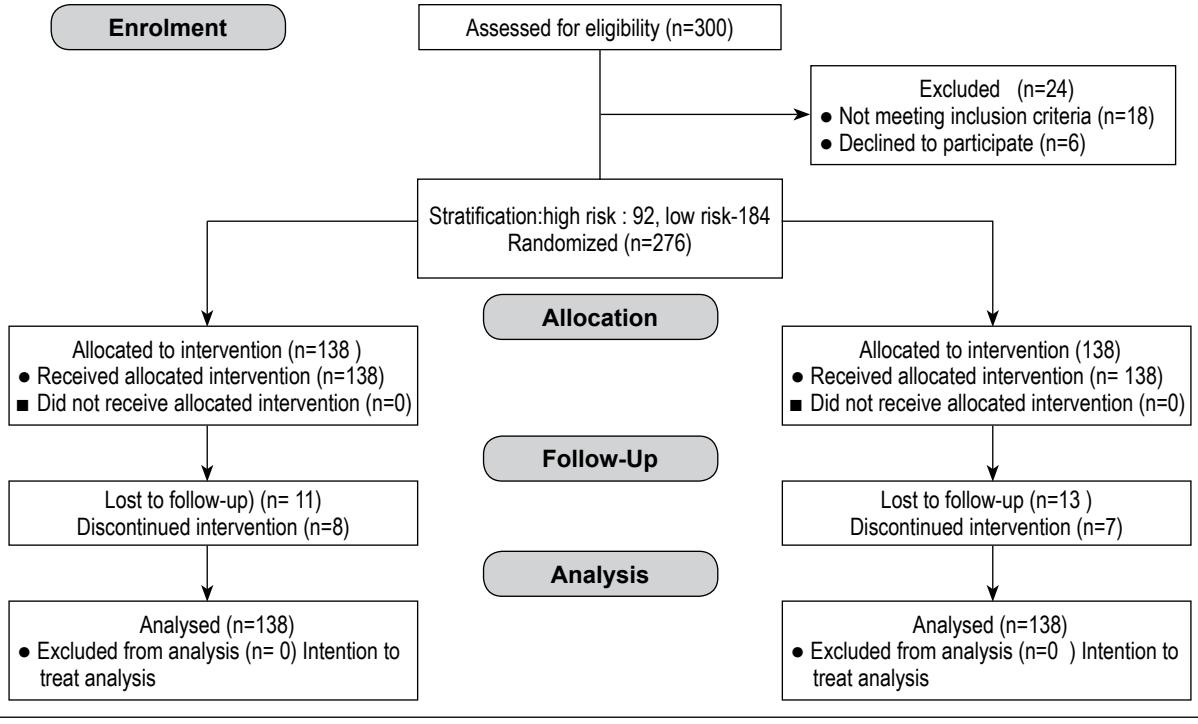
Birth weight of newborn, Apgar score (1,5 min) and other neonatal complications were noted.

The primary outcome measure was incidence of Gestational hypertension, Pre-eclampsia and Eclampsia. Secondary outcome measures were incidence of HELLP syndrome, abruptio placentae, PROM, preterm labour, meconium stained liquor and Incidence of preterm birth, small for gestational age, perinatal loss, low apgar score at 1 and 5 minutes, need for NICU admission.

Analysis was done by intention to treat. Excel version 7 (Microsoft, Redmond, WA, USA) and MedCalc version 11 (MedCalc Software,Ostend, Belgium)were used for statistical analyses. Results were reported as mean ± SD, number (percentage), and median (range). Student t, $\chi 2$, and Fisher exact tests were performed to compare variables. Mean and median differences with 95% confidence intervals(CIs) and relative riskswith 95% CIswere calculated for outcome parameters as appropriate. $P < 0.05$ was considered statistically significant.

Results

Figure 1: CONSORT Diagram showing flow of participants through the study



Three hundred women attending antenatal OPD were subjected to screening for eligibility and 18 were found ineligible due to various medical and obstetric complications and 6 women declined to participate. Two hundred and seventy six women were subjected to subsequent stratification based on risk assessment and high risk factors for development of preeclampsia were found in 92 women. Subsequently, both the high risk and low risk group were separately randomized into the study and control groups for the intervention. (Figure 1)

Majority of cohorts in our study were 20-29 years; nearly half were primigravida. For both the categories, there were no statistically significant difference between study and control group from demographic point of view (Table 1).

We found no significant difference related to maternal primary outcome between study and control group in both high risk & low risk cohorts. Severe gestational hypertension, severe pre-eclampsia and eclampsia were extremely infrequent in all the cohorts. Milder form of the disease was encountered in approximately 20% and 26% women of study and control group respectively in the high risk cohorts while the corresponding figure in the low risk cohorts were 9% and 13% respectively. Overall incidence of hypertensive disorders of pregnancy was slightly lower in vitamin supplemented than non-supplemented groups irrespective of risk factors,the differences ,however failed to reach statistical significance (high risk : p=0.35, RR 0.67, 95%CI 0.34-1.33 & in low risk : p=0.36, RR 0.69, 95%CI 0.34-1.40).(Table 2)

Among our cohorts in both high & low risk categories, no significant difference was observed relating to secondary maternal outcomes in terms of incidence of preterm labour, PROM, abruptio placentae, oligohydraminos, meconium stained liquor between study and control groups. (Table 3)

We observed that, overall incidence of perinatal complications were marginally lower in the cohort that received vitamins, more so in the high risk category compared with the study group who received placebo; the difference was, however not significant statistically (23.91% vs. 34.78%, p=0.35). We did not find any difference in 1 and 5 minute Apgar score ,incidence of preterm birth, RDS, NICU admission and perinatal loss between study and control group. We also found that incidence of SGA was slightly lower in the study group of both high and low risk categories compared with the respective placebo groups, the difference was not, however, significant (high risk: 8.16% vs. 12.24%, p=0.74; low risk: 6.52% vs. 8.7%, p=0.78). (Table 4)

Discussion:

Supplementation with antioxidants, mainly vitamins C and E, have been proposed as a potential preventive strategy on the basis of a role of increased oxidative stress in the pathogenesis of preeclampsia.

In the present study, we compared the incidence and severity of pre-eclampsia as the primary outcome among women with or without risk factors of the said disease who were randomly assigned to vitamins C and E supplementation and placebo groups.

We observed that overall incidence of hypertensive disorder of pregnancy were marginally lower in the group that received vitamin supplementation compared with those who received placebo in both high and low risk categories; the differences, however, did not reach statistical significance (high risk: 21.74% vs. 32.61%; p=0.35; low risk: 11.96% vs. 17.39%, p=0.36). In agreement with our observation, Alice R. Rumbold et al[8] in a similar study involving larger cohorts , failed to show any reduction in the incidence of preeclampsia in the vitamin supplemented cohorts {6% [n=935] in vitamin group vs 5% [n=942] in control group, p=0.57)}. Similar findings were reported by A Huria et al[9] (mild preeclampsia 2.8% [n=107] in vitamin group vs. 5.5% [n=109] in placebo group; severe preeclampsia 1.87% vs 4.59% in the two groups respectively, both were statistically insignificant) and Prof L Poston et al[10] (incidence of pre-eclampsia : 15% [n=181] vs 16% [n=187] in the two groups respectively, RR 0.97 [95% CI 0.80–1.17]) in their randomized controlled trials. The conclusion of WHO multicentric trial[11] and three meta-analysis of related RCTs[12–14] were also similar to our study.

On the contrary, Chappell et al.[15] in a randomized controlled trial, on 283 high risk women (identified as being at increased risk for preeclampsia because of an abnormal two-stage uterine artery Doppler analysis or a previous history of preeclampsia) found that Vitamin supplementation was associated with a

Table 1 : Demographic profile

Parameters	High Risk Group			Low Risk Group		
	Study (n=46)	Control (n=46)	p-value*	Study (n=92)	Control (n=92)	p-value*
Age in years, Mean ± SD	26.07 ± 7.06	25.85 ± 6.91	0.88	25.83 ± 3.67	25.51 ± 3.49	0.55
Gravidity, Median (range)	1.5 (1-4)	2 (1-4)	0.62	2 (1-4)	1.5 (1-4)	0.72

Table 2 : Maternal Primary Outcome : Incidence of Hypertensive Disorders of Pregnancy

Primary Maternal Outcome	High Risk Group				Low Risk Group			
	Study (n=46)	Control (n=46)	RR (95% CI)	p-value*	Study (n=92)	Control (n=92)	RR (95%CI)	p-value*
Mild Gestational Hypertension	2 (4.35%)	4 (8.70%)		0.67	4 (4.35%)	5 (5.43%)		0.73
Severe Gestational Hypertension	0	1 (2.17%)		0.31	1 (1.09%)	2 (2.17%)		0.56
Mild Pre-Eclampsia	7 (15.22%)	8 (17.39%)		0.78	4 (4.35%)	7 (7.61%)		0.52
Severe Pre-Eclampsia	1 (2.17%)	1 (2.17%)		1	1 (1.09%)	2 (2.17%)		0.56
Eclampsia	0	1 (2.17%)		0.31	1 (1.09%)	0		0.31
TOTAL	10 (21.74%)	15 (32.61%)	0.67 (0.34-1.33)	0.35	11 (11.96%)	16 (17.39%)	0.69 (0.34-1.40)	0.36

*Chi-square test

Table 2 : Maternal Secondary Outcomes

MATERNAL SECONDARY OUTCOMES	HIGH RISK GROUP				LOW RISK GROUP			
	Study (n=46)	Control (n=46)	RR (95% CI)	p-value*	Study (n=92)	Control (n=92)	RR (95%CI)	p-value*
HELLP syndrome	0	0	1 (0.02-49.36)	1	0	0	1 (0.02-49.87)	1
PROM	2 (4.35%)	2 (4.35%)	1 (0.15-6.80)	1	3 (3.26%)	4 (4.35%)	0.75 (0.17-3.26)	0.70
Preterm labour	3 (6.52%)	1 (2.17%)	3 (0.32-27.79)	0.62	4 (4.35%)	3 (3.26%)	1.33 (0.31-5.79)	0.70
Abruptio placentae	0	1 (2.17%)	0.33 (0.01-7.98)	0.31	0	0	1 (0.02-49.87)	1
Oligohydraminos	2 (4.35%)	2 (4.35%)	1 (0.15-6.80)	1	1 (1.09%)	2 (2.17%)	0.50 (0.05-5.42)	0.56
Meconium stained liquior (MSL)	1 (2.17%)	2 (4.35%)	0.50 (0.05-5.32)	0.56	3 (3.26%)	2 (2.17%)	1.5 (0.26-8.77)	0.65
Others	1 (2.17%)	2 (4.35%)	0.50 (0.05-5.32)	0.56	3 (3.26%)	4 (4.35%)	0.75 (0.17-3.26)	0.70

Table 4 : Neonatal Outcome

NEONATAL OUTCOME	High Risk Group			Low Risk Group		
	Study (n=46)	Control (n=46)	p-value*	Study (n=92)	Control (n=92)	p-value*
Preterm birth	4 (8.16%)	4 (8.16%)	1	7 (7.61%)	6 (6.52%)	0.77
SGA	4 (8.16%)	6 (12.24%)	0.74	6 (6.52%)	8 (8.70%)	0.78
RDS	1 (2.04%)	2 (4.08%)	0.56	3 (3.26%)	5 (5.43%)	0.72
NICU admission	2 (4.08%)	3 (6.12%)	0.65	3 (3.26%)	4 (4.35%)	0.70
Perinatal loss	0	1 (2.04%)	0.31	1 (1.09%)	0	0.31
Total perinatal complications	11 (23.91%)	16 (34.78%)	0.35	20 (21.73%)	23 (25.0%)	0.72

significant reduction in the maternal concentrations of biomarkers for preeclampsia [plasminogen-activator inhibitor (PAI)-1-to-PAI-2 ratio] and a 54% reduction in the risk of preeclampsia. The results of the study may be altered due to type I statistical error because such study was not powered for preeclampsia. Also, in contrast to our observation, Kirtan Manoj Vyas et al[16] found significant reduction in the incidence of gestational hypertension (5 % vs. 10% : vitamin vs. placebo; significant) and Preeclampsia (00% vs. 5% in the two groups respectively; significant). There was 66% reduction in risk of hypertensive disorders of pregnancy in their study cohort. This difference with our study may be due to the following reason: a combination of aspirin and antioxidants were used in the study group and use of aspirin may have benefited the women of study group in preventing pre-eclampsia. Apart from that, study subjects were younger,only primigravidae and cohorts were small in number (40 in each group).

There were no difference among the supplemented and non-supplemented groups in terms of the secondary maternal outcomes as preterm labour, oligohydramnios, meconium stained liquor etc. Similar observations were reported by Alice R. Rumbold et al[8] (incidence of preterm PROM: 3.2% in vitamin group vs 2.4% in control group; abruptio placentae: 0.3% in vitamin vs 0.1% in placebo group; major PPH 2.9% in vitamin vs 3% in control group, all were non-significant). Contrastingly, Kirtan Manoj Vyas et al[16] observed lower incidence of oligohydraminos and meconium stained liquor in cohorts receiving vitamins (oligohydraminos : 2.5% in study vs 10% in control [RR=0.25] ; MSL;0% in study vs. 7.5% in control group [OR=0.13]).Additional supplementation with aspirin may have improved the outcome of women in the study group.

Agustín CONDE-AGUDELO et al,[12] in a meta-analysis, found the risk of abruptio placentae to be significantly lower in the group of women who received vitamins C and E than among women who received placebo (0.6% vs 1.0%; RR 0.63, 95% CI 0.43 to 0.94; I^2=0%; five trials, 13,075 women). That we did not encounter abruptio placentae in our cohorts, could be due to smaller sample size.

Apart from a marginal non-significant reduction of incidence of overall perinatal complication and SGA newborns, perinatal outcome did not show any improvement in the supplemented group compared with placebo. Similar to our observations, Alice R. Rumbold et al[8] found no difference in terms of severe birth asphyxia . In agreement with our findings, Prof L Poston et al[10] reported that incidence of Small for gestational age (SGA) did not differ between aforesaid groups.

In contrast, Kirtan Manoj Vyas et al[16] found that low birthweight <2.5 kg was significantly low in the group who received antioxidants (0% vs. 25% : study vs. control; p<0.05). This also may be due to addition of Aspirin along with vitamins in their study group.

Inspite of strong theoretical basis of the hypothesis that antioxidants would prevent pre-eclampsia, it is unclear why supplementation with vitamins C and E during pregnancy did not reduce the risk of preeclampsia and its sequels in the present study. First, it is possible that although oxidative stress plays a ajor role in the pathophysiology of preeclampsia, it is not important in the causal pathway of the disorder. Thereby, it would be unlikely that reversing the oxidative stress would reduce the risk of preeclampsia. Secondly, oxidative stress could be relevant to the pathogenesis of preeclampsia in only a subgroup of women, with no appreciable benefit of vitamins C and E for the entire population.

Limitations of our trial is that it is underpowered for primary outcomes. Lack of resources and fixed time limit prevented us from increasing the samle size. Second, the long-term consequences of exposure of mothers and their children should have been relevant, but it was beyond the scope. Finally, we could not investigate the effect of supplementation with vitamins C and E in women with indices of oxidative stress and deficiency of antioxidants.

Conclusion

Antioxidants (Vitamin C and Vitamin E) supplementation in pregnancy did not cause significant reduction of incidence of pre-eclampsia and other hypertensive disorders of pregnancy, as well as it did not alter other maternal and fetal outcomes in women with or without risk factors .However, larger cohorts with specific quantitative indices of oxidative stress is necessary for more evidences.

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Original Article: Gynecology

Ventouse: A Useful Instrument in Gynaecological Operations

Dr. Jayanta Ray,[1] Dr. Salil Bindu Chakraborty,[2] Dr. Suparna Sutradhar[3]

Abstract

Ventouse is a useful instrument for conducting instrumental deliveries. Though it was introduced for conducting instrumental deliveries by Malmstrom in the year 1954, till date, the instrument is not applied in Gynaecological major surgeries like Hysterectomies for large fibroid uterus and exploratory laparotomies for big ovarian tumours. Often difficult, prolonged and manipulative gynaecological surgeries lead to more tissue injuries and blood loss ultimately cause increased morbidities. More over all grasping clamps are traumatic, which causes blood loss and messy operating field. Silastic ventouse cup is suitable for rapid application for exteriorization of big tumours of ovaries and uterus. Silastic ventouse cup provides very good atraumatic grip on smooth ovoid tumours. This instrument was used on 120 subjects with ovarian tumours and surgeries for uterine leiomyoma, over 10 years. Application of silastic ventouse cup for exteriorization of ovarian tumours and big fibroid uterus, and clean surgeries were successfully conducted on 115 subjects. Two applications were abandoned due to dense adhesions of the tumours. In 2 cases, only partial exteriorization could be achieved as those tumours were very big in sizes, and in one operation the ovarian tumour got ruptured at the site of ventouse attachment. This application of silastic ventouse cup in gynaecological major surgery is very encouraging and needs to be studied more extensively for further improvements.

Keyword: Silastic Ventouse cup application, Ovarian Tumour, Leiomyoma Uterus, Exteriorization.

Background

There is no denial that ventouse is very useful equipment for instrumental deliveries. But such useful equipment is not tried in gynaecological procedures. May be due to thought block, that it could not be introduced in gynaecological operations. It is often very difficult to exteriorise big ovarian tumours or Leiomyoma uterus during the gynaecological surgeries. Particularly ovarian tumours often get

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ruptured in this process leading to up staging if happens to be malignant.[1,2] Big tumours of ovaries or uterus requires to be exteriorised to get space for clean surgery and trying to do that often-required bigger incisions and difficult manipulations, leading to accidental trauma to adjacent tissues and viscera besides accidental rupture of Ovarian tumour. Such unwanted intraoperative problems in the beginning of the surgery leads to messy and difficult surgery. So, to minimise such complications during surgery, applications of ventouse is tried over last ten years on 120 patients. Since 1954, Ventouse is a well-established safe method for instrumental delivery of live foetus.[3] Therefore, traction applied by silastic ventouse cup to exteriorise pelvic lump by Gynaecologist will not be an issue of concern.

Material and Method

This intervention was conducted in a tertiary care hospital of North East India. The study was conducted over a period of ten years from 2007 to 2017. Total numbers of subjects recruited in the study was 120. Patient selection was done based on preoperative clinical diagnostic evaluations of Size, surface and mobility of the Ovarian or Uterine lump. Final decision of the ventouse application to exteriorisation of the Ovarian tumour or Uterian Fibroid was taken after per operative evaluation following laparotomy by subumbilical midline vertical incision. This protocol is strictly followed to ensure study subject's safety from the procedure. For rapid application of ventouse,[4,5,6] only silastic ventouse cups were used in this study. The ventouse cup was applied at the furthest area from the pedicle or attachment. Suction was created by connecting the ventouse cup to ordinary OT suction pump. After exteriorisation of the Ovarian Tumour or the Uterian Fibroid, rest of the operative procedures are completed as per standard conventional procedure.

Result:

The study was conducted on total 120 subjects. Duration of the study was ten years from2007 to 2017. Out of all the study subjects, in 2 subjects complete exteriorisation of the Ovarian tumour could not be done completely. As in both the subjects, the ovarian tumours were very big with irregular surfaces and were adherent to adjacent structures. However, the tumour was partially exteriorised and with gradual decompression by suction of the tumour content, later whole of the tumour was exteriorised and operations were completed successfully. In one case, the ovarian tumour ruptured at the site of ventouse cup attachment, during exteriorisation process. But most of the content of the tumour was sucked in by the ongoing suction of the ventouse cup. As a result, only minimum contamination occurred. In two other subjects, applications were abandoned due to strong adhesions of the tumours to nearby structures which prevented mobility of the tumours. In rest of the 115 subjects (Table 1), applications and exteriorisations were smooth. Only in three operations the abdominal incisions required extensions above umbilicus, as the tumours were non- compressible. Blood loss was less than conventional manipulative surgeries. Recovery from surgery were smooth. Out of total 120 subjects, 74 tumours were of ovarian origin and rest 46 were uterine leiomyoma. Majority tumours (89) were less than the size of 20 weeks gravid uterine size.

Table 1: Distribution of cases and successful exteriorization

	Number of cases	Successful exteriorization
Ovarian Tumour	74	69
Fibroid Uterus	46	46
Total	120	115

Table 2: Distribution of ovarian tumours after gross clinical evaluation

Type of Ovarian Tumours	Number
Ovarian Teratoma	19
Big Ovarian Cystic Tumour	55
Total	74

Table 3: Distribution of benign and malignant ovarian tumours after histopathological report

	Number
Benign Ovarian Tumours	58
Malignant Ovarian Tumours	16
Total	74

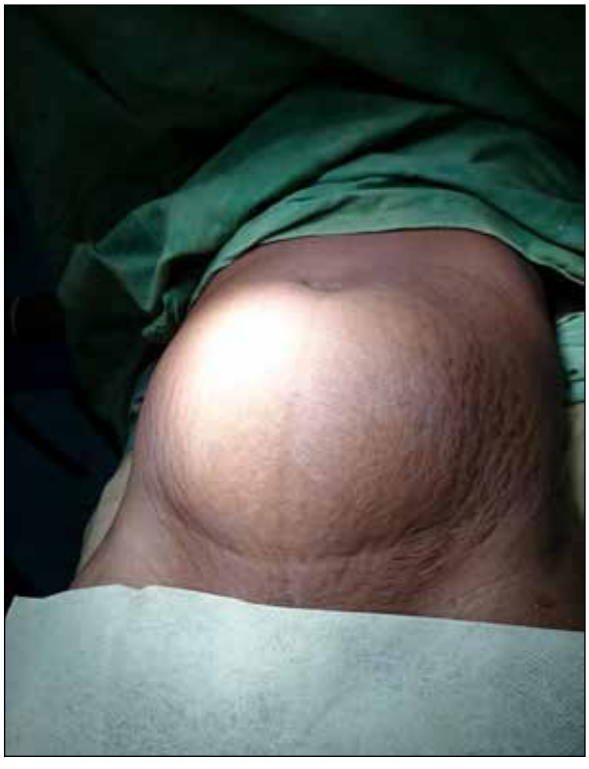
Table 4: Size of Tumours; related to gravid uterus in weeks

Size	Number
< 20	89
≥ 20 weeks	31
Total	120

Discussion

Performing clean surgery depends on proper exposure and technique. However often a simple surgery become very messy and prolonged due to improper

incision and difficult manoeuvre7. In gynaecological surgeries of big ovarian tumour and at times uterine leiomyoma pose great difficulty to exteriorise without extending the incision and rupturing the ovarian tumour capsule. It is very difficult to grasp Large tumours with conventional instruments as these instruments are often traumatic. Silastic ventouse cup is easily applied under direct vision, on smooth surface of both ovarian tumours and big uterine fibroids, which provide a good atraumatic grip on the tumours for traction. Ventouse makes it easy to exteriorise the tumour with very simple manoeuvre. In most of the procedures incision does not required to be extended as with good grip on the tumour which could be gradually squeezed out through the standard laparotomy incision. Application of ventouse on the surface of ovarian tumour or uterine fibroids are comparatively easier than conventional cephalic applications in instrumental vaginal deliveries. Once the tumour is exteriorised the rest of the surgery often become very easy due to proper and clean exposure. Chance of accidental rupture and spillage is grossly minimised. The time of surgery is reasonably decreased and due to less manipulation tissue injury also reduced which led less blood loss and faster recovery. Use of ventouse in gynaecological surgery is very encouraging but it needs further studies.



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Original Article: Gynecology

First line ovulation induction agent in PCOS-Clomiphene or Letrozol- A Randomized Trial

Dr. Vinu Choudhary,[1] Dr. Manisha Choudhary,[2] Dr. Usha Shekhawat[3]

Abstract

Clomiphene citrate (CC) remains the usual first line therapy for these cases of PCOD. The primary objective of this study was to test the hypothesis that letrozole as a primary ovulation induction agent will generate higher pregnancy rates than CC in anovulatory women with PCOS.

Methodology: A total of 200 patients, 100 in each letrozol and CC group were included which met the inclusion criteria.Study was conducted in Dept. of Reproductive Medicine and medical genetics, at Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan from august 2016 to december 2017.

Results: Endometrial thickness was 7.0 mm with CC group and 8.4 mm with letrozol which was found to be statistically significant ($p<0.05$). Monofollicular development in our study with CC group was 42 % in comparison to 79 % with letrozol group which is statistically significant. In our study ovulation rate was high in letrozol group (78%in letrozol versus 85% in CC).

In conclusion, our results of randomized trial suggest that letrozole is as good as CC in terms of ovulation rate. The endometrial thickness was significantly better in the letrozole group.

Introduction

Polycystic ovary disease (PCOD) is the most common cause of anovulatoryinfertility. Clomiphene citrate (CC) remains the usual first line therapy for these cases. Because of its structural similarity to estrogen, CC competes for and binds to hypothalamic estrogen receptors triggering the normal compensatory mechanisms of reduced estrogen negative feed back

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ending in pituitary gonadotropin release. When administered to already ovulatory woman CC increases GnRH pulse frequency, while in anovulatory woman with PCOS in whom GnRH pulse frequency is already abnormally high, CC increases pulse amplitude rather than frequency.

CC is known for the discrepancy between ovulation and pregnancy rates (73 versus 36%). In other words, only half of the patients who ovulate will conceive. This discrepancy has been traditionally attributed to interference with estrogen receptors function in other tissues such as endometrium and cervix. Furthermore CC is not always successful in achieving ovulation as the so called clomiphene resistance is encountered in up to 20% of patients.Traditional alternatives for these cases included; gonadotropin therapy, and laparoscopic ovarian diathermy (LOD). Gonadotropin therapy is associated with the risk of ovarian hyperstimulation syndrome, and multiple pregnancy, and LOD is associated with the risk of post-operative adhesions and decreased ovarian reserve.

Aromatase inhibitors (AI) are the group of drugs that block estrogen production, without affecting estrogen receptors. The resultant low ambient estrogen level reduces the negative feed-back on hypothalamus and pituitary and stimulates FSH release.[1,2] In addition, intra-ovarian accumulation of androgenic estrogen precursors is thought to increase ovarian FSH receptors. Superior conception rates and less multiple pregnancies than CC were therefore expected. Letrozole was the first aromatase inhibitor to be used for this indication. Studies on letrozole were mostly conducted on clomiphene resistant cases, and because of its short history in this respect, concepts like letrozole resistance and failure were not addressed.

Originally Letrozole was approved by the United States Food and Drug Administration (FDA) for the treatment of local or metastatic breast cancer that is hormone receptor positive or has an unknown receptor status in postmenopausal women. Letrozole has been used for ovarian stimulation by fertility doctors since 2001 because it has fewer side-effects than clomiphene (Clomid) and less chance of multiple gestation. A study of 150 babies following treatment with letrozole or letrozole and gonadotropins presented at the American Society of Reproductive Medicine 2005[1,3] Conference found no difference in overall abnormalities but did find a significantly higher rate of locomotor and cardiac abnormalities among the group having taken letrozole compared to natural conception. A larger, follow-up study with 911 babies compared those born following treatment with letrozole to those born following treatment with clomiphene. That study also found no significant difference in the rate of overall abnormalities, but found that congenital cardiac anomalies was significantly higher in the clomiphene group compared to the letrozolegroup. Despite this, India banned the usage of letrozole in 2011, citing potential risks to infants but it again came in practise from February 2017 after clearance from medical board.

The primary objective of this study was to test the hypothesis that letrozole as a primary ovulation induction agent will generate higher pregnancy rates than CC in anovulatory women with PCOS.

Methodology

A total of 200 patients, 100 in each letrozol and CC group were included which met the inclusion criteria. Study was conducted in Dept. of Reproductive Medicine and medical genetics, at Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan from august 2016 to december 2017 Inclusion criteria

1. Patient of primary / secondary infertility.
2. BMI upper range = 29.9 kg/m2
3. Age between 21 to 32 years of age group
4. Informed and written consent of patient.
5. Clinical or ultrasound criteria of PCOS to be fulfilled.
6. LH below 7

Exclusion criteria

1. Patients with H/O tuberculosis, endometriosis.
2. BMI >= 30 kg/m2

Patients were given tablet clomiphene 100 mg or letrozol5 mg from day 3 to day 7 of menstrual cycle depending on randomization by coputer generated table. Follicular monitoring was done to assess size of dominant follicle and hormonal profile LH was done on day 3 of menstrual cycle and serum E2 Level on day of trigger. Endometrial thickness was assessed on day of HCG trigger.

Data analysis was done using SPSS computer software system, Value of p<0,05 was taken as statistically significant.

Results

Table 1. Demographic profile

Demographic features	Clomiphene citrate (n=100)	Letrozole (n=100)
Age (years)	26.7	27.2
BMI (kg/m^2)	25.4	25.9
Waist to Hip ratio (WHR)	0.91	0.95
Duration of infertility (years)	3.1	3.5
Type of infertility		
Primary infertility	77	71
Secondary infertility	23	29

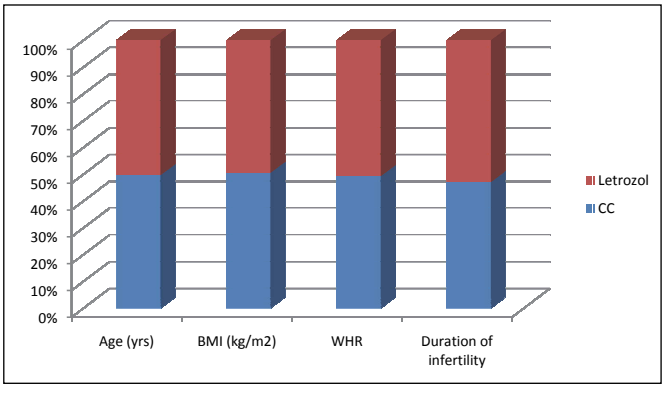


Table 2. Ultrasound parameters

Parameters	CC (n-100)	Letrozole (n=100)
Monofolliculardevepment	42	79
Multifollicular development	58	21
Endometrial thickness on day of HCG trigger (mm)	7.0	8.4
Average duration of induction (Days)	18	15

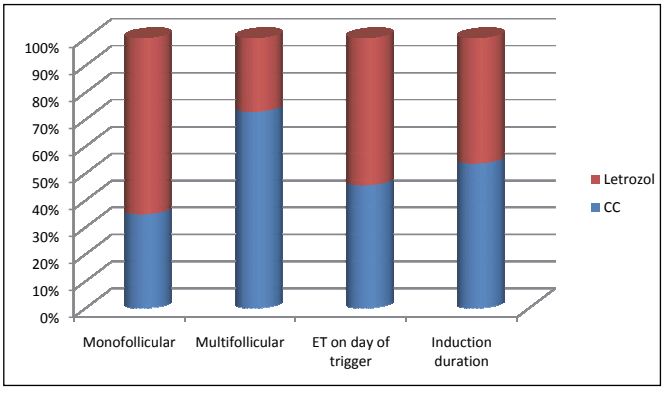


Table 3. Hormonal Profile

Parameters	CC (n=100)	Letrozole (n=100)
LH day 3	5.6	6.2
E2 on day of ovulation (pg/ml)	380	188
Serum progesterone on day 21 (ng/ml)	12.5	14.8

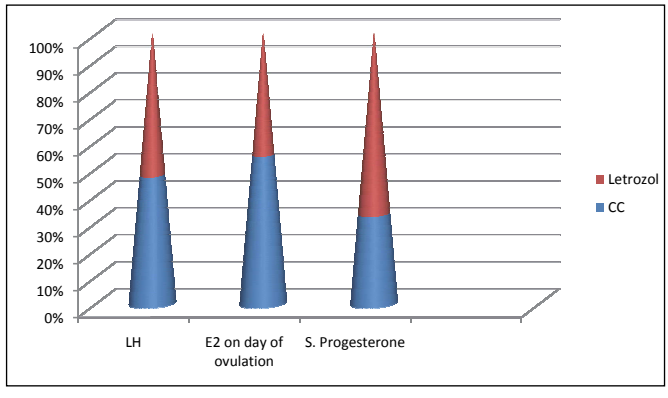
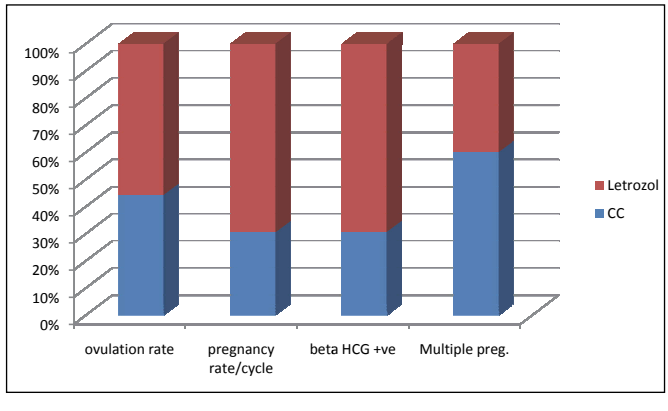


Table 4. Outcome of Treatment

Outcome	CC (n=100)	Letrozole (n=100)
Ovulation rate	78	85
Clinical Pregnancy rate/cycle	9.2	15
Beta HCG positive/cycle	11	16
Multiple pregnancy	03	02
Cumulative pregnancy rate	16.16	29.3



Discussion

For many years, CC has been used as the first treatment of choice for patients with PCOS. It is generally accepted that CC reduces uterine receptivity, and thus reduces the chances of conception. It is associated with endometrial thinning in 15–50% of patients,[7] probably due to estrogen receptor depletion. Furthermore, the use of CC may block estrogen receptors in the cervix,

producing a negative effect on the quality and quantity of cervical mucus.[9,10] Inappropriate development of the endometrium is associated with low implantation rate and early pregnancy loss due to luteal phase defect. With letrozole, estrogen production is eventually advanced by the induced FSH release, but in contrast to the use of CC, the hypothalamus is able to respond to estrogen feedback with a negative feedback mechanism.[13,14] This helps in modulating an overzealous discharge of FSH, which in turn is more likely to result in a mono-follicular ovulation with moderate estrogen concentration. Letrozole also has an added positive effect, as it may increase follicular sensitivity to FSH through amplification of FSH receptor gene expression. Although letrozole creates an estrogen-deficient environment, it has no negative effect on the endometrium and cervix due to its short half-life (45 h). In contrast, CC has a long half-life (2 weeks),[9,15] and it is possible that CC concentrations could accumulate over subsequent cycles. This could lead to increased risk of adverse endometrial or cervical mucus changes. Therefore, ovulation induction by letrozole is superior to CC in terms of follicular growth and endometrial response.

In our study demographic profile of patients in Clomiphene citrate and letrozol group both were comparable to each other.

Endometrial thickness was 7.0 mm with CC group and 8.4 mm with letrozol which was found to be statistically significant ($p<0.05$). Badawy et al.[4] in their study of 438 patients with 1063 cycles, one of the largest studies comparing CC and letrozole, reported statistically significantly higher endometrial thickness in CC group (9.2 ± 0.7) vs. letrozole (8.1 ± 0.2, P = 0.021). They attributed this effect to greater number of mature follicles and higher serum E2 levels. Mitwally and Casper found letrozole associated with greater endometrial thickness. This is supported by recent studies reporting adequate endometrial thickness during letrozole treatment (Mitwally and Casper,[5] 2001; Al-Omari et al., 2004;[11] Atay et al., 2006[12]). Furthermore, unlike CC that accumulates in the body because of its long half-life (2 weeks),[15] letrozole is rapidly eliminated due to its short half-life (45 h), leading to late follicular rise in circulating oestrogen thereby enhancing endometrial development with subsequent increase in the chances of pregnancy (Young et al., 1999).[14] Cortinez et al.[16] found normal morphologic features of endometrium and full expression of pinopodes during implantation window when letrozole was used. Few studies have shown no significant difference between the two groups with regard to effect on endometrium. In a recent study by Banerjee et al.,[13] 147 Indian women with PCOS were compared between letrozole (2.5 mg) Vs. clomiphene (100 mg). Mean endometrial development was 8.72 ± 11.41 mm in letrozole and 8.78 ± 1.16 mm in CC group (P = 0.004).

Monofollicular development in our study with CC group was 42 % in comparison to 79 % with letrozol group which is statistically significant which is expected and corroborated by Badawy,[4] Bayar et al,[6] Zeinalzadeh et al.[8] In contrast study conducted by Fisher[9] et al bound high rate of multifollicular development 72% in letrozolversus 68% in CC group. Serum E2 level was found to 380 pg/ml in clomiphene citrate as compared to 188 pg/ml in letrozole group which was found to be statistically significant.

The largest study comparing CC to LE was that of Badawy et al. (438 infertile women 1063 cycles). In this study the incidence of multifollicular response was unexpectedly high for the given dose (6.8 versus 4.4 follicles for CC, and LE, respectively) The study reported non significant advantage of CC in ovulation and pregnancy rates. This is contradictory to the only meta-analysis; conducted which concluded that letrazol has significant advantage over CC in ovulation and pregnancy rates. In our study, we have also found that the mean total E2 on the day of hCG administration was significantly higher in CC group as compared with letrozole group.

In our study ovulation rate was high in letrozol group (78%in letrozol versus 85% in CC). Rashida Begam et al.[7] reported higher ovulation rate (62.5%) with letrozole compared with 37.50% with CC. Mitwally and Casper using 2.5 mg/day of letrozole achieved 75% and 100% ovulation in anovulatory and ovulatory patients respectively. Higher ovulation rate with letrozole was also reported in other studies. Ovulation rate was found to be comparable as reported by Bayer et al., (81% in letrozole group versus 85% in CC group). Others reported similarly, Badawy et al.[4] (CC 70.9%, Let 67.5%), Bayar et al.[6] (CC 74.7%, Let 65.7%), and M. Zeinalzadeh et al.[8] (CC 72%, Let 86%). In majority of the studies, no

statistically significant difference is found between CC and letrozole in ovulation rate.

Pregnancy rate per cycle was found to higher in letrozolgroup (15 in letrozol versus 9.2 in CC) which was found to statistically significant in the present study. Zeinalzaden et al., with 107 women, both reported slightly better pregnancy rates with letrozole; however, no statistically significant difference between the two groups. Cumulative pregnancy rate was high in letrozol group (29% in letrozol versus 16 % in CC group) again found to statistically significant and also supported by study conducted by Badawyetal.

Conclusion

In conclusion, our results of randomized trial suggest that letrozole is as good as CC in terms of ovulation rate. The endometrial thickness was significantly better in the letrozole group. Letrozole was also found to be superior than CC in terms of clinical pregnancy rate. Therefore, letrozole is a safe and better alternative to CC in ovulation induction protocol for patients of anovulatory PCOS, and it may be considered as a first-line treatment for ovulation induction in these patients.

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Case Report: Gynecology

Cutaneous Ciliated Cyst of The Vulva, A Case Report

Capt Vidisha Khanna,[1] Dr.mukesh Agrawal,[2] Dr. Akina Prakash,[3] Dr. Srivatsa Prakhya[4]

Abstract

Introduction: Benign cysts of the vulva have been reported most common being bartholin's cyst followed by epidermoid cyst.[1] Cutaneous ciliated cysts (CCC) are a rare entity seen in women in 2nd or 3rd decade, predominantly in the lower limb.[2] There is no mention of CCC over vulva. Here we report a case of benign cyst of the vulva which turned out to be a cutaneous ciliated cyst on histopathology.

Key words: cutaneous ciliated cyst, benign vulval lesions.

Case Report

A 42 year old multiparous lady presented to the gynecology OPD of Military Hospital, Faizabad with complaint of a painless lump over the vulva since four years. Her main concern was dyspareunia and a worry about possibility of malignancy. On examination there was a soft , non tender well defined mass around 2 by 2 cm lateral to frenulum. It was continuous with a 2 cm lump seen at the introitus inner to the left labium. There was no lymphadenopathy. Excision was planned under spinal anesthesia.

A linear skin incision was given over the bulge of the lump lateral to the frenulum and the cyst enucleated. The cyst contained thick transparent fluid and was in continuation with the mass on the inner side of the labia as expected. Postoperative period was uneventful.

Histopathology section showed cystic lesion in the dermis lined by ciliated columnar epithelium, with focal areas showing papillary configuration. The wall also showed lymphocytes, plasma cells and foamy macrophages. A diagnosis of cutaneous ciliated cyst of the vulva was made.

Discussion

Cutaneous Ciliated Cyst (CCC) is an unusual benign cystic lesion of subcutaneous tissue the epithelium of which is reminiscent of the fallopian tube lining or lining of the airway and middle ear. These cysts are usually noticed as a painless lump. They are believed to arise from heterotopic mullerian epithelium. There have been case reports of CCC mostly in lower limb and a case of CCC over perineum of 60 year old male.[3] It was observed that CCC rapidly increases in size during pregnancy, which suggest that the lesion could be sensitive to hormonal stimulation.[4] Another evidence for the same would be that in some of the cases, these epithelial cells exhibited intranuclear ER and PR positivity.[5] Excision of the lesion is reported to be curative. Multifocal lesions or recurrences have not been reported in the literature till date.[6]

Conclusion

The case was unique as it was expected to be a sebaceous cyst clinically, but it turned out to be a rare lesion

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Figure 1: the appearance of the vulval mass

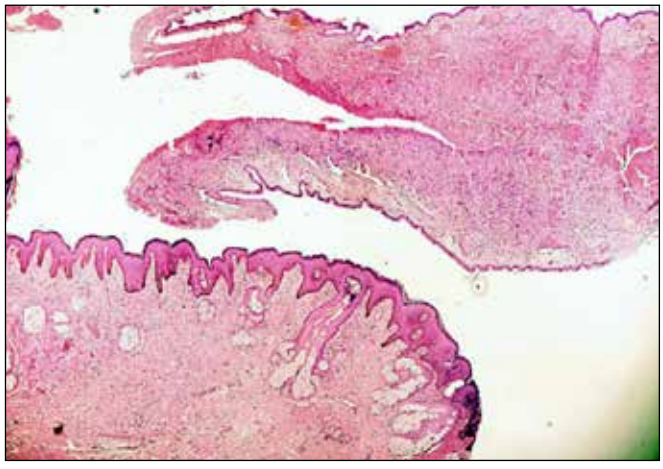

Figure 3: Cystic lesion lined by ciliated epithelium (H&E, 4x)

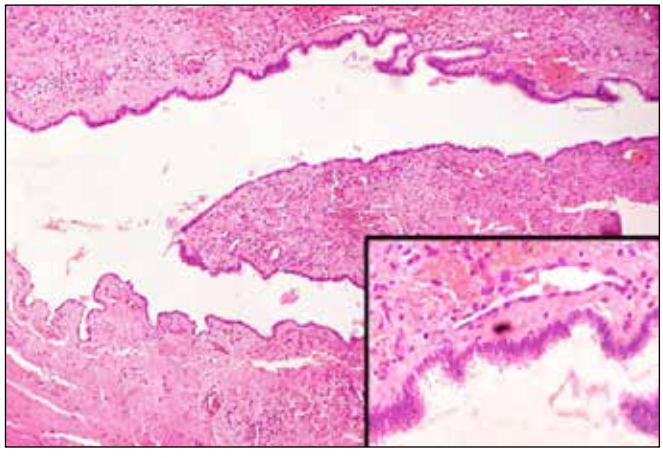

Figure 4: Cyst lined by ciliated columnar epithelium (Inset showing the epithelial lining in 40x) , with wall showing lymphocytes and macrophages (H&E, 10X)

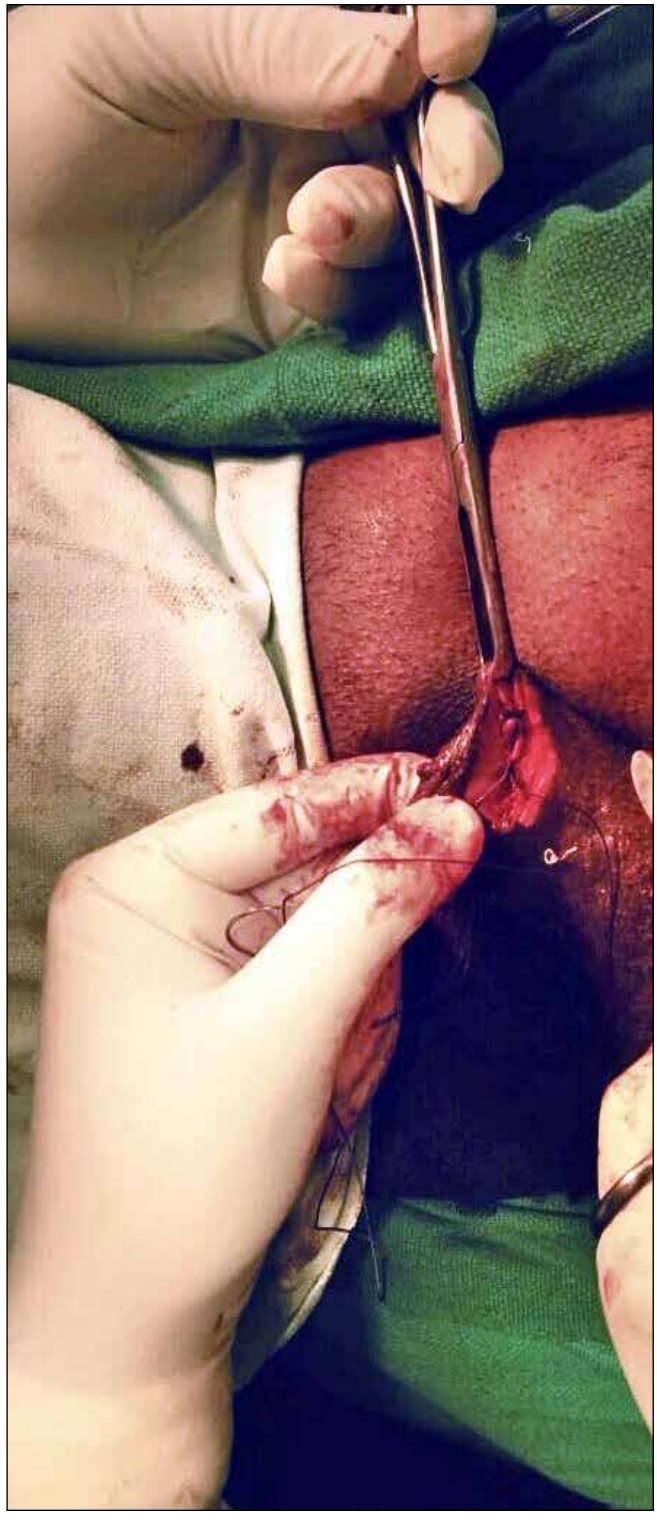

Figure2:closure of the bed after removal of the cyst

on histopathology. Management in both cases would remain the same, that is excision when symptomatic.

Acknowledgement

We acknowledge the commanding officer of Military Hospital, Faizabad for his encouragement and cooperation.

We also acknowledge Lt Col Ritesh Dubey, anesthesiologist for making the surgery possible

Disclosure

The authors firmly state that there is no interest to disclose

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Case Report: Gynecology

Microperforated Hymen : A case of Delayed Diagnosis

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Dr. Madhavi M Gupta,[3] Dr. Chetna Arvind Sethi[4]

Abstract

Microperforate hymen is a congenital condition where there is failure of hymen to perforate completely resulting in a tiny opening in it. Microperforate hymen is frequently mistaken for an imperforate hymen. The tiny opening on the obstructive vaginal membrane is quite difficult to visualize. We report a case of 20year female with Microperforate hymen who had complaints of heaviness during menses and difficulty in using tampons.

Introduction

Imperforate hymen is a congenital condition with incidence of 1 in 1000. While imperforate hymen completely covers the vagina, a microperforate hymen has small pin head size opening. Embryologically, it is because of the failure of the cells of vaginal plate to break down and failure of the hymen to dissolve in utero. Because of the hymen to canalise and perforate completely in the perinatal period can result in varying anomalies including imperforate, microperforate, cribriform (sievelike), navicular (boatlike), or septated hymen.[1] Microperforate hymen is a congenital obstructive vaginal membrane with a tiny opening. It is usually detected long after menarche as the cases are often overlooked and not diagnosed in time. Few cases of it have been detected before puberty. This condition may be diagnosed late as the female does not present with primary amenorrhoea, cyclical pain, hematometra and hematocolpos as the menstrual blood is able to pass through the tiny opening although slowly. The patient may present with recurrent episodes of vulvovaginitis, difficulty in using tampons and feeling of obstruction in the passage of vagina, dyspareunia, prolonged duration of menstrual cycles. The treatment of this technique is hymenotomy by giving cruciate incision. Others methods of progressive dilatation by hegars dilators have also been described.[2]

We report this patient with microperforate hymen who had complaints of heaviness during menses and difficulty in using tampons.

Case Report

A 20 year old unmarried female presented in outpatient department with complaints of heaviness during menses and difficulty in using tampons.

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Figure 1. External female genitalia showing a probe inserted in the hymenal microperforation as well as urethral catheterization

She had regular menstrual cycles with scarce flow and prolonged duration of menstrual flow. General examination and abdominal examination were normal. External examination of genitalia showed imperforate hymen but there was no bulge. In view of her menstrual history, the patient was called during menses to confirm the site from where she menstruates. The tiny opening in the hymen was seen in the lower left quadrant of the membrane (at 4 o'clock position). She was planned for hymenotomy under general anaesthesia. After doing urethral catheterisation, the small opening was enlarged with help of dilators (Figure 1). A cruciate incision was given in the hymen enlarging this opening. On per speculum examination, normal cervix was visualised (Figure 2).The edges were sutured with 3 0 vicryl to the hymenal ring to avoid restenosis (Figure 3). Patient was put on antibiotics and discharged. She had patent vagina at one month follow-up.

Discussion

Microperforate hymen is a variant of obstructive hymenal membrane with a tiny opening, which impairs vaginal intercourse and menstrual hygiene consequently impacting negatively the quality of life of the young women. The type of abnormality depends

Figure 2. Normal cervix is visualised after hymenotomy

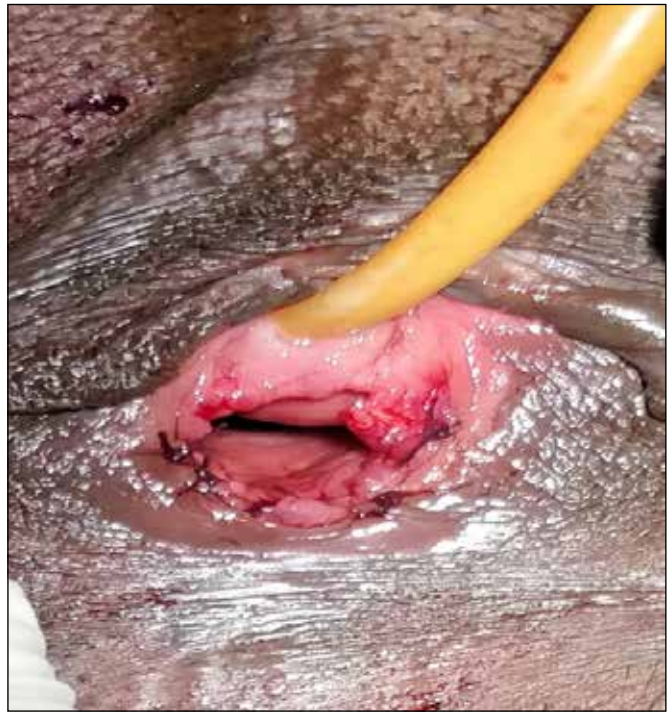

Figure 3. Final result after hymenotomy. The hymenal membrane edges, which were sutured to avoid restenosis.

on the degree of failure of canalisation of hymenal membrane at the extreme caudal aspect. These hymenal abnormalities are classified by Gynecology and Obstetrics and adopts the Vagina Cervix

Uterus Adnexa associated malformation (VCUAM) classification. It divides hymenal occlusions in subtotal (V1a) and complete (V1b) hymenal obstruction.[3] There are only few cases reported in the literature. The association with genetic factor is not found.

Microperforate hymen has not been found to be associated with urinary tract abnormalities although few cases also had bifid clitoris, polydactyly, ureter duplication, hypoplastic kidney.[4] Few cases of Microperforate hymen has been reported with vaginal septa mostly those under 1 cm.[3,5]

Microperforate hymen may be asymptomatic and the diagnosis may be delayed. The females may present at start of menarche when there is inability of menstrual blood to completely flow out. They may also present with difficulty in putting tampons, vaginal creams, suppositories and difficulty in intercourse or there may be history recurrent episodes of vulvovaginitis.[6] Because the accumulated blood in the vagina is exposed to infection , they may present with pelvic abscess and pyocolpos.[7] Due to difficulty in coitus, it may favour abnormal sexual behaviour such as urethral coitus.[8] Primary infertility may be the first presenting symptom in few cases.[9] Although the normal intercourse is not feasible, but there have been cases of pregnancy reported in microperforate women.[10] On the other hand, imperforated hymen may be responsible for primary amenorrhea, cyclic pelvic pain, symptoms due to compression of the bladder or intestine, hematocolpos, hydrometrocolpos, hematometra and hematosalpinx.[4]

Differential diagnosis includes imperforated hymen, Mayer-Rokitansky syndrome, transverse vaginal septum and labial adhesions.[5] In this setting, physical examination and imaging workup may furnish the correct diagnosis.

Treatment is directed in opening the subocclusive membrane through the tiny opening. The type of incision may vary from cruciate, vertical, central and stitching the edges to the hymenal ring as to avoid stenosis. Foley's catheter can be put in the operated hymenal opening for two weeks to avoid restenosis.

We conclude that this entity is often missed and there is delay in diagnosis because there is lack of awareness by clinicians and external genitalia examination is not a routine practice. The emphasis is on examination of such females during menstrual period so that this condition is not missed and efforts should be made to diagnose this before puberty and thus preventing further complications.

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