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High Dose Versus Low Dose Oxytocin for Augmentation of Delayed Labour in Obese Women: A Randomized Clinical Trial

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ABSTRACT

Buckhound: For augmentation of delayed labour, high- or low-dose oxytocin can be used, but the evidence for promoting high-dose in obese women is weak. In obese women, labour progress is often delayed, leading to a caesarean section despite labour augmentation with synthetic oxytocin.

Objecitve: Our study aims to evaluate the effect of high dose oxytocin augmentation in spontaneously labouring obese women.

Patients and methods: We included 202 patients who were randomly assigned to two groups in a randomized controlled trial (RCT) study. Patients were divided into two groups: Group I (low dose oxytocin) were given 2 mU/minutes (min) of oxytocin, which was gradually increased by 2 mU/min every 30 minutes until adequate uterine contractions were achieved. Patients in Group II (high dose oxytocin) were given 4 mU/min of oxytocin, which was gradually increased by 4 mU/min every 30 minutes until adequate uterine contractions were achieved.

Results: Both management were equally effective in clinical data with no significant difference between the two studied groups (P>0.05). Difference in oxytocin dose, duration of oxytocin, and uterine tachysystole between the two groups was statistically significant. The rates of caesarean section did not differ between groups (8.7% and 8.1%). The rates of instrumental vaginal births were similar. In terms of neonatal outcomes, there were no differences.

Conclusion: Except for reducing labour duration, high dose oxytocin had no advantages over low dose oxytocin in labour augmentation. Low-dose oxytocin is less likely to cause uterine hyperstimulation, making it a safer option.

Keywords: Caesarean section, Obese women, Oxytocin.

INTRODUCTION

Obesity is one of the biggest public health problems of the 21st century as it increases the risk of many co-morbid medical conditions. Obesity in pregnancy places women at higher risk of obstetrical complications during pregnancy, delivery and puerperium. Obesity is a risk factor for cesarean delivery, failed induction of labour and labour dystocia**,** and prolonged labour curves [(1)].

Intrapartum care of obese women is usually associated with more frequent interventions as early hospital admission, artificial rupture of membranes (AROM), epidural anesthesia, and oxytocin augmentation compared to normal-weight women [(2)]**.** However, they are still more likely to end labour with unplanned cesarean delivery (CD) [(3)], with subsequent increased risk for major postoperative complications [(4)]**.**

Oxytocin infusion in labour could be used for augmentation until women's contraction patterns become stronger and more regular and cervical changes occur. There is emerging evidence that obese women need more oxytocin to augment labour compared to lean women. This could be attributed to the effect of higher maternal body mass index (BMI) that is linked to decreased myometrial efficiency[(5)] and higher neonatal birth-weights [(6)]**.**

However, protocols for oxytocin dosing are not individualized by maternal BMI in most of management guidelines. Therefore, obese women are more likely to "fail" oxytocin augmentation, leading to increased risk of unplanned CD due to slow labour progress [(2)]**.**

Previous studies in this issue illustrated conflicting results. Some of them concluded that higher maternal BMI has been associated with larger median oxytocin dose and longer oxytocin infusion durations [(7)]**.** On the other hand, in another study including women with spontaneous labour onset who had either cesarean or vaginal deliveries, oxytocin augmentation was less effective among obese compared to normal-weight women, more often failing to prevent unplanned CD for slow labour progress [(8)]**.**

Additionally, a study by **Adams and Drassinower** [(9)] revealed that obese women require higher doses of oxytocin to achieve a vaginal delivery and they recommend further research to determine whether higher oxytocin protocols should be considered for obese women or not.

This study aims to determine the effect on caesarean section rate of high-dose versus low-dose oxytocin for augmentation of delayed labour, scheduled vaginal or cesarean delivery rates, maternal and fetal outcomes in term pregnancies in obese women.

PATIENTS AND METHODS

Study setting and duration: Assiut Woman's Health University Hospital, Assiut between the 1st of September 2018 and 31st of August 2020.

Type of the study: The current study was a prospective registered, double-blind, randomized clinical trial. The obstetrician and participant were blinded of the study groups.

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Study participants: All low-risk labouring obese women who were attended the labour ward during the study period were invited to participate in the study if they met the inclusion criteria.

Inclusion criteria: Age: above 18 years, spontaneous onset of labour, BMI ≥ 30 kg/m^2, gestational age ≥ 37 weeks, singleton pregnancy, cephalic presentation, reassuring fetal heart rate monitoring, inefficient uterine contractions during active labour, and women who accepted to participate in the study.

Exclusion criteria: Non-reassuring fetal assessment at the time of recruitment, women received cervical ripening agents, any patients contraindicated for vaginal delivery, multiple gestations, malpresentation, previous cesarean delivery, patients with cardiac diseases, pre-eclampsia or any other medical disorders, fetal demise, intrauterine growth restriction, estimated fetal weight ≥ 5000 grams, and pre-labour rupture of membranes > 24 hours.

Sample size calculation:

Sample size was calculated using the Open-Epi software program, version 2.3.1. A recent study by **Carlson *et al.*** [10] reported the mean duration between low dose oxytocin augmentation initiation to vaginal delivery in obese women was 6.2 hours with a standard deviation 3.87 hours**.** We hypothesized that high dose oxytocin will be effective in shortening this duration by 25%. Using two sided chi-square (χ^2) test with α of 0.05, a total sample size of at least 210 women in both groups (105 in each group) using 80% power would be necessary to detect 25% reduction in our primary outcome with the use of high dose oxytocin.

Recruitment:

On admission to the labour ward, full patient history was reported and a general and obstetric examination was performed. Patients were weighed and had their height measured wearing light clothes and no shoes. BMI was calculated. Patients were classified according to 3 obese classes (kg/m^2) categories: obese I (30.0-34.9), obese II (35.0-39.9) and obese III (≥40.0).

Pregnancy duration was calculated from the first day of the last menstrual period, confirmed by first trimester ultrasonography. Active labour was defined as at least three regular uterine contractions lasting at least 40 seconds within a 10-minute period with cervical dilatation of at least 3 cm.

Labour-management protocols, including the timing and frequency of cervical examinations performed during labour was fixed using the modified WHO partograph. Evaluation of uterine contractions every 30 minutes was carried out by abdominal palpation for calculation of the frequency and duration. Vaginal examination was performed every 2 hours for assessment of cervical dilatation.

Hypotonic inertia was defined as inefficient uterine contractions (less than three contractions lasting less than 40 seconds within a 10-minute). If diagnosed, amniotomy was performed and re-assessment of uterine contractions was performed after 30 minutes. If they still inefficient, patients were randomized to one of the two study groups for oxytocin infusion.

Randomization:

A statistician prepared a computer generated random tables and placed the group allocation in serially numbered closed opaque envelopes. The envelopes were opened only by the principal investigator according to the order of delivery of women. After acceptance of eligible women to participate in the study, we assigned them randomly mostly in a 1:1 ratio to both study groups. Allocation was never changed after opening the envelopes. All patients and managing obstetricians were blinded to the allocation to avoid bias.

Patients were divided into two groups:

Group I (low dose oxytocin): patients received IV infusion of 5 Units of oxytocin/500 mL lactated ringer solution. Starting rate was 2 mU/min, incrementally increase by 2 mU/min every 30 minutes until achievement of adequate uterine contractions.

Group II (high dose oxytocin): patients received IV infusion of 5 Units of oxytocin/500 mL lactated ringer solution. Starting rate was 4 mU/min, incrementally increase by 4 mU/min every 30 minutes until achievement of adequate uterine contractions.

The doses were adapted from the ACOG guidelines 2009 for oxytocin use during delivery[11]**.**

Ethical consent:

An approval of the study was obtained from Assiut University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data were analyzed using SPSS software Chicago, IL, USA, version 25. Comparison between categorical variables in both groups was done by Chi-square test and continuous variables were compared using Student T-test. Quantitative data were expressed as mean ± SD (Standard deviation). For statistical analysis. We tested the data for normality by Shapiro-Wilk test. Survival curves depicted the number of deliveries over time within each BMI category were used. Univariate Cox-regression models were performed. P-value <0.05 was considered as a significant value.

RESULTS

Demographic data in study groups showed that there was non-significance difference between study groups regarding age, gestational age, BMI, residence, work, and mode of delivery (Table 1).

Table (1): Demographic data in the two studied groups

Items		Group				p value
		Low dose of oxytocin (N=103)		High dose of oxytocin (N=99)		
Age (years)		28.97 ±5.64		29.27 ±6.00		0.728
Gestational age (weeks)		38.42 ±0.69		38.52 ±0.71		0.238
Parity		1.79 ±1.19		1.81 ±1.29		0.998
BMI (kg/m^2)		34.27 ±2.79		34.21 ±2.38		0.846
		n	**%**	**n**	**%**	
Residence	Rural	30	29.1%	29	29.3%	0.979
	Urban	73	70.9%	70	70.7%	
Working status	Housewife	36	35.0%	35	35.4%	0.952
	Working	67	65.0%	64	64.6%	
Mode of delivery	Vaginal	103	100.0%	99	100.0%	1.000
	CS	0	0.0%	0	0.0%	

Values are presented as mean ± standard error of mean or number (%)

Table (2) shows that there was a non-significant difference between groups regarding oxytocin dose. However, there was significant difference concerning duration oxytocin and uterine tachysystole.

Table (2): Oxytocin given by treatment in the two studied groups

Items	Group											
	Low dose						High dose					
	Obese I		Obese II		Obese III		Obese I		Obese II		Obese III	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Oxytocin dose till onset of uterine contraction mU/min	148.62	106.12	281.82	146.57	324.00	131.45	186.77	151.36	250.91	217.09	420.00	301.99
p-value between subgroup	**<0.001**						**0.031**					
p-value	0.560											
Duration oxytocin till onset of uterine contraction (min.)	49.38	20.15	70.91	22.27	78.00	16.43	37.26	15.06	43.64	19.97	60.00	24.49
p-value between subgroup	**<0.001**						**0.023**					
p-value	**<0.001**											
	n		**%**				**n**		**%**			
Uterine tachysystole[a]	35		34.0%				50		50.5%			
P value	**0.017**											

a: Definition of tachysystole: "more than five uterine contractions in 10 min for longer than 20 min"

There was a statistically insignificant difference between groups as regard maternal outcome (**Table 3).**

Table (3): Maternal outcome in the two studied groups

Items	Group				P value
	Low dose of oxytocin (N=103)		High dose of oxytocin (N=99)		
	n	%	n	%	
Maternal distress	1	1.0%	0	0.0%	1.000
Maternal injure	11	10.7%	12	12.1%	0.826
Bl. Trans	1	1.0%	0	0.0%	1.000
Postpartum hemorrhage	2	2.0%	0	0.0%	0.498
Admission. To ICU	0	0.0%	0	0.0%	

Table (4) shows that there was non-significant difference between both study groups regarding fetal outcome.

Table (4): Fetal outcome in the two studied groups

Items		Group				p value
		Low dose of oxytocin (N=103)		High dose of oxytocin (N=99)		
Birth weight (gm)		3069.23 ±383.69		3103.03 ±216.51		0.751
Apgar at 1 min		9.27 ±0.45		9.26± 0.44		0.883
Apgar at 5 min		10.0 ±0.00		10.00 ±0.00		1.000
Duration of hospital stay (days)		3.47 ±0.52		3.52 ±0.60		0.334
		n	**%**	**n**	**%**	
NICU		1	1.9%	4	4.0%	0.438
Fetus gender	Male	54	52.4%	53	53.5%	0.779
	Female	49	47.6%	46	46.5%	

Values are presented as mean ± standard error of mean or number (%)

The estimated mean and median active phase duration until vaginal delivery in hours in low dose group are shown in table 5. The survival probability is lower for obese III at all-time points so they are less likely to deliver vaginally.

Table (5): Survival analysis using Kaplan-Meier curve showing survival of onset of active labour until vaginal delivery in low oxytocin group for 3 obese classes (kg/m^2) categories: obese I (30.0-34.9), obese II (35.0-39.9) and obese III (≥40.0)

Means and Medians for Survival Time[a]								
	Mean[b]				Median			
			95% Confidence Interval				95% Confidence Interval	
Group 1	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Obese I	4.745	0.178	4.397	5.093	4.000	0.237	3.536	4.464
Obese II	5.273	0.316	4.654	5.891	5.000	0.381	4.252	5.748
Obese III	6.400	0.773	4.885	7.915	6.000	1.095	3.853	8.147
Overall	4.997	0.159	4.686	5.308	5.000	0.291	4.430	5.570
a. Group = **Low dose**								
b. Estimation is limited to the largest survival time if it is censored.								

Additionally, in high dose group, the estimated mean and median active phase duration until vaginal delivery in hours are shown in table 6. The survival probability is lower for obese III at all-time points so they are less likely to deliver vaginally.

Table (6): Survival analysis using Kaplan-Meier curve showing survival of onset of active labour until vaginal delivery in high oxytocin group for 3 obese classes (kg/m^2) categories: obese I (30.0-34.9), obese II (35.0-39.9) and obese III (≥40.0)

Means and Medians for Survival Time[a]								
	Mean[b]				Median			
			95% Confidence Interval				95% Confidence Interval	
Group2	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
Obese I	4.484	0.162	4.166	4.802	4.000	0.132	3.741	4.259
Obese II	4.667	0.290	4.099	5.234	4.000	0.203	3.603	4.397
Obese III	6.000	0.000	6.000	6.000	6.000	.	.	.
Overall	4.626	0.147	4.337	4.915	4.000	0.114	3.776	4.224
a. Group = High dose								
b. Estimation is limited to the largest survival time if it is censored.								

Finally, the estimated mean oxytocin dose mU/min until vaginal delivery for the 3 subgroups of the high oxytocin group is shown in Table 7.

Table (7): Survival analysis using Kaplan-Meier curve showing survival of oxytocin dose reached to achieve vaginal delivery in high oxytocin group for 3 obese classes (kg/m^2) categories: obese I (30.0-34.9), obese II (35.0-39.9) and obese III (≥40.0)

	Mean				P value
			95% Confidence Interval		
Group2	Estimate	Std. Error	Lower Bound	Upper Bound	
Obese I	182.835	15.815	151.837	213.833	**<0.001**
Obese II	303.409	29.645	245.304	361.513	
Obese III	413.333	83.504	249.666	577.000	

A hazard ratio (HR) >1 indicates an increased number of vaginal deliveries over time compared to the reference group; a shorter duration of labour. A HR < 1 indicates a decreased number of vaginal deliveries over time compared to the reference group (Table 8).

Table (8): Cox regression showing the hazard ratio (HR) of vaginal birth in the defined body mass index (BMI) groups

		95.0% CI for HR	
	HR	Lower	Upper
Obese I	1		
Obese II	0.559	0.404	0.773
Obese III	0.387	0.180	0.836

DISCUSSION

In the present study, our main goal was to evaluate the effect of high dose oxytocin augmentation in spontaneously labouring obese women. In the current study, mean age of presentation was 28.97 ±5.64 years in Low dose oxytocin group and 29.27 ±6.00 years in High dose oxytocin group. While mean Gestational age was (38.42 ±0.69) weeks in Low dose oxytocin group and (38.52 ±0.71) weeks in High dose oxytocin group. Pregnant women demonstrated higher BMI (34.27 ±2.79 vs 34.21 ±2.38) in both groups. Other previous studies have described that the range of maternal age is between the 27 to 31years [12, 13]. These results corroborate the ideas of **Roloff *et al.*** [7] who suggested that mean age of low dose group was 29.0 (4.8) years while that of high dose group was 29.0 (4.6) years.

We described the results of pre labour data; it was found that there was no statistically significant difference regarding rupture of membrane and head position. In contrast, duration of 1st stage (hours) and duration of 2nd stage (min) were significantly increased in Low dose oxytocin group than in High dose oxytocin group. As regard duration of 1st stage (hours), we reported that duration of active phase (hours) was 4.98 ± 1.60 in Low dose oxytocin group and 4.51 ±1.30 in high dose oxytocin group. Concerning duration of 2nd stage (min); in Low dose oxytocin group its estimated mean was 10.48 ± 3.04 and in High dose oxytocin group its estimated mean was 9.64 ± 2.54. These results are in agreement with **Lassiter *et al.*** [12], which showed a longer labour period for women with a BMI over 30 kg/m^2. **Norman *et al.*** [14] reported a cohort of over 5,000 women demonstrating that women with BMIs greater than 30 kg/m^2 had a longer duration of labour.

When compared to women with a BMI of <30 kg/m^2, women with a BMI of over 30 kg/m^2 had a longer time interval until delivery, required more oxytocin, and had a higher cesarean delivery rate [15]. Similarly, **Selin *et al.*** [13] noticed that labour duration was 23 min shorter with a high-dose regimen of oxytocin (mean difference -23.4 min, 95% CI -45.1 to -1.5).

Interestingly, the pathophysiology of obesity's impact on labour is unknown. Myometrium obtained at the time of elective cesarean delivery from overweight women showed decreased contractility compared to normal weight women in a study conducted by **Zhang *et al.*** [16]. **Garabedian *et al.*** [17] discovered that as BMI increased, so did oxytocin receptor expression. In theory, this could lead to increased uterine contractility in obese women, but clinically, this is not observed.

Our study found that head position was occiput anterior (95.1%), in Low dose oxytocin group, while the head position in High dose oxytocin group was occiput anterior (96.0%). Also, our results go in line with the results by **Selin *et al.*** [13] who noticed that the frequency of occiput anterior was 62 (87.7%) in Low dose group versus 60 (87.6%) in High dose group. According to labour outcome findings, it was found that there was no statistically significant difference concerning to mode of delivery and indication for caesarean section. The results of this study showed that, there was a statistically significant difference in oxytocin dose, duration oxytocin and uterine hyperstimulation.

Moreover, there was no difference between the Low dose and High dose of oxytocin groups with respect to the frequency of CS, (8.7%) versus (8.1%) respectively. There were no significant differences in the rate of indication for caesarean section between the two regimens. The main indication for operative caesarean section was fetal distress in the high dose oxytocin group (66.7% versus 100%) and failure to progress in the low dose oxytocin group (33.3% versus 0.0%).

These results reflect those of **Selin *et al.*** [13] who also found that there was no difference in the frequency of CS between the high-dose and low-dose groups, with 80 of 647 women (12.4 percent) versus 80 of 648 women (12.3 percent). The primary indication for CS was failure to progress in both the high-dose (55.0%) and low-dose (62.5%) groups, but the difference was not statistically significant (difference 7.5 percent, 95 percent CI 24.0 to 9.0). This is comparable to the incidence of CS in obese reported by **Akgol *et al.*** [18] who reported a 6.1% women delivered by CS in obese.

Our study also found that duration of oxytocin was significantly prolonged in the Low dose oxytocin group (57.67 ±23.27 min). compared to High dose oxytocin group (40.30 ±17.75 min). Besides, we reported uterine hyperstimulation in 34.0% of Low dose oxytocin group versus 50.5% in high dose oxytocin group.

A retrospective cohort study by **Adams and Drassinower** [8] reported that in the class III obesity group, the mean duration of oxytocin augmentation to achieve vaginal delivery was 12.76 hours, with a cumulative oxytocin dose of 12453.8 mU, compared to the reference group, which had 9.44 hours of oxytocin use and a cumulative oxytocin dose of 7625.9 (p.0001). Women in the class III obesity group were significantly more likely to need a maximum oxytocin dose of more than 20 mU/min to achieve a vaginal delivery (24.6 percent vs 10.4 percent, p<0.001).

Women with a BMI of 35 or higher received significantly more oxytocin during the first three hours of augmentation in successfully treated labour arrest, according to **Soni and colleagues** [19].

Maeder *et al.* [20] conducted a retrospective review on 280 women undergoing induction due to postdates who were overweight (BMI 25 to 29.99 kg/m^2) or obese (BMI 30 kg/ m2). The results were consistent with previous study demonstrating increased oxytocin quantities, but they disagreed with **Maeder *et al.*** [20] who demonstrated longer labour durations and higher cesarean rates. Interestingly, the study looked at units of oxytocin per hour of infusion, and while obese women received more oxytocin during labour, they may

not have received enough units of oxytocin per hour of infusion.

This comes in agreement with another study by **Selin *et al.*** [13] which compared high and low dose oxytocin regimens for labour augmentation in 1,295 women and found no differences in cesarean, vaginal, or instrumental deliveries between the two groups. In high dose oxytocin, they found a significant increase in the incidence of uterine tachysystole. However, they discovered that high dose oxytocin was related with shorter labour duration when compared to low dose oxytocin. In contrast, a study from China revealed that 900 pregnant women were admitted to the hospital for delivery and found a significant reduction in the risk of cesarean and instrumental deliveries with a significant increase in spontaneous vaginal deliveries in the high dose oxytocin group. Furthermore, they found no significant difference in labour duration or uterine hyperstimulation risk between the two oxytocin regimens [21]. Interestingly, the results of another RCT showed no significant differences between high and low dose oxytocin in the incidence of cesarean and vaginal delivery as well as instrumental delivery, and in the risk of uterine hyperstimulation [22].

In the current study, the neonatal outcome of the study participants were similar in birthweight, Apgar score, length of NICU stay, and percent of newborns admitted to the NICU (1.9% vs 4.0%) in low dose vs high dose of oxytocin groups respectively. This comes in agreement with a study by **Kenyon *et al.*** [23] who reported that regarding NICU admission risk, there were no significant differences between high and low doses oxytocin according to their findings. This outcome is contrary to the **Neerukonda *et al.*** [24] who found that high oxytocin doses were associated with an increase in the number of neonates admitted to the NICU.

Finally, the log-rank test was used to compare the Kaplan Meier (KM) curves for three BMI (kg/m^2) categories: obese I (30.0-34.9), obese II (35.0-39.9), and obese III (40.0). To compare the oxytocin necessary to achieve vaginal delivery, a Cox proportional-hazards model was fitted and variables associated with increased oxymax dose were adjusted. In univariate Cox analysis, we found an increased HR of vaginal delivery, resulting in an increase oxytocin dose until vaginal delivery with increasing BMI. Compared with obese I women, the HR of caesarean delivery was 0.559 (95%CI 0.404-0.773) for obese II and 0.387 (95%CI 0.180-0.836) among obese women.

There are similarities between the attitudes expressed by **Hermesch *et al.*** [25]**.** They found that according to KM analysis, BMI is significantly related to the oxytocin required to achieve vaginal delivery (VD). When censoring by taking CD into account, the oxymax required to achieve a VD rate of 75% differed by BMI: normal and overweight at 20 mU/min, obese I at 24 mU /min, obese II at 28 mU /min, and obese III at 36 mU /min ($p<0.001$). BMI and magnesium were significantly associated with a higher oxymax to achieve VD in the multivariable model. Obese III women were 59 percent less likely than normal weight women to have VD at any oxytocin dose [HR 0.41 (0.3-0.6) p0.001].

Also, **Ellekjaer *et al.*** [26] noticed a hazard ratio (HR) of 0.83 (95 percent confidence interval [CI] 0.73–0.96) for overweight (BMI 25–29.9 kg/m^2) women compared to normal-weight women in univariate Cox analysis, implying a longer duration of active labour for overweight women compared to normal-weight women.

CONCLUSION

Except for reducing labour duration, high dose oxytocin had no advantages over low dose oxytocin in labour augmentation. Low-dose oxytocin is less likely to cause uterine hyperstimulation, making it a safer option. To avoid unnecessary hyperstimulation and fetal distress, a low-dose oxytocin regimen is recommended. More research is needed to back up our findings.

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