Immediate versus Delayed Oxytocin Infusion following Amniotomy for Induction of Labor in Primiparous Women:A randomized controlled trial

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Abstract: Objective: The aim of the current study was to compare immediate versus delayed (after 4 hours) oxytocin infusion following amniotomy in primiparous women planned for induction of labor at term singleton pregnancy. **Methods:** The current randomized controlled trial was conducted at Ain Shams University Maternity hospital The study included primiparous women admitted to the labor/delivery ward for planned induction of labor of a term living singleton pregnancy (at gestations between 37 and 41^{+6} weeks). The recruited women were randomly allocated into one of two groups: group I including women who had amniotomy and immediate oxytocin infusion; and group II including women who had amniotomy and delayed oxytocin infusion (after 4 hours). **Results:** A total of 120 women were included in the study. The mean gestational age was 40.08 ± 1.33 weeks (range: 37.29 – 41.71 weeks). The median oxytocin-to-onset of the active phase, oxytocin-to-delivery and onset of the active phase-to-delivery intervals were slightly lower in women of group II when compared to women of group I, but not to a significant level. The median amniotomy-to-onset of the active phase and amniotomy-to-delivery intervals were significantly higher in women of group II when compared to women of group I. The median VAS for labor pain was significantly higher in women of group I when compared to women of group II. There were no significant differences between neonates of both groups regarding 1-min and 5-min Apgar scores. **Conclusion:** Early oxytocin infusion, following amniotomy for induction of labor in primiparous women, seems to be advantaged over delayed oxytocin infusion (after 4 hours) by the significantly shorter duration of labor and better women satisfaction, without any significant adverse impact on the maternal and perinatal outcome.
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1.Introduction:

Induction of labor is a common obstetric practice that represents nearly 20% of the work at any labor/delivery ward [1]. The standard widely-used method for induction of labor is amniotomy and oxytocin infusion, often preceded by cervical ripening with a prostaglandin or a prostaglandin analogue agent [2]. It has been proven that, in women presenting with pre-labor rupture of the membranes, induction of labor with immediate oxytocin infusion was the method with least perinatal or maternal morbidity, and without any alteration of the delivery outcome, when compared to expectant (delayed) management or induction with prostaglandins [3]. There is, however, no recommendation regarding the timing of onset of oxytocin infusion following amniotomy during induction of labor in women with intact fetal membranes. The conclusion reached by authors of a Cochrane systematic review on that issue was that data on effectiveness and safety of amniotomy plus oxytocin and the timing of oxytocin (whether immediate or delayed) are lacking, and randomized clinical trials regarding this intervention are highly needed [4]. The aim of the current clinical trial was to compare immediate versus delayed (after 4 hours) oxytocin infusion following amniotomy for primiparous women planned for induction of labor at term singleton pregnancy.

2. Methods

The current randomized controlled trial was conducted at Ain Shams University Maternity hospital during the period between November 2009 and December 2010. The study protocol was proposed in accordance to the Declaration of Helsinki for the Principles of Ethical Medical Research, and was approved by the Ethical Research Committee, Obstetrics and Gynecology Department, Ain Shams University. Participant women had to sign an informed written consent after thorough explanation of the purpose and procedure of the study. The study included primiparous women admitted to the labor/delivery ward for planned induction of labor of a term living singleton pregnancy (at gestations between 37 and 41^{+6} weeks).

The majority of included women, being primiparous, had an initial modified Bishop score < 6. In order to improve the modified Bishop score, one or

two ripening doses of a prostaglandin analogue (misoprostol) [25 µg vaginal tablet], 4 hours apart. Women were recruited and amniotomy was performed only after the Bishop score reaches ≥ 6. Women above 35 years old, and those in active labor, or who had pre-labor ruptured fetal membranes, women with malposition (diagnosed by ultrasonography), abnormal liquor volume, abnormal non-stress test were not recruited in the trial. The recruited women were randomly allocated into one of two groups: group I including women who had amniotomy and immediate oxytocin infusion; and group II including women who had amniotomy and delayed oxytocin infusion (after 4 hours). Oxytocin infusion was started at a rate of 10 mIU /min with gradual titration of the dose (through doubling every 30 min) till reaching an adequate uterine contractions (3-4 contractions every 10 min, each lasting 45-60 seconds). Randomization was performed using a computer-generated randomization system. The allocation labels were kept in serially numbered opaque envelopes that were opened only after recruiting the patient. Women were partographically followed up till delivery, with fetal monitoring according to the protocols of Ain Shams University Maternity Hospital regarding the active management of labor. Primary outcome was time to onset of the active phase of labor and time to delivery. Secondary outcomes included perception of labor pains, uterine hyperstimulation, mode of delivery, patient satisfaction and neonatal outcome. Perception of labor pain was measured using a 0-to-10 visual analogue scale (VAS) with 0 pointing to no pain, and 10 pointing to the maximum pain. Uterine hyperstimulation was defined as presence of ≥ 5 contractions every 10 min or any contraction lasting more than 90 seconds [5]. Maternal satisfaction was measured using the 5-point Likert scale [6] (very satisfied, satisfied, indifferent, unsatisfied and very unsatisfied). Satisfied women were those who reported being "very satisfied" or "satisfied".

Sample size justification

Sample size was calculated using EpiInfo® version 6.0, setting the power at 80% and two-sided confidence level at 0.05. The primary outcome was the vaginal delivery within 12 hours. Data from a pilot study [7] showed that the proportion of successful induction of labor within 12 hours was 58.1% in the delayed group and 77.1% in the immediate group. Calculation according to these values produced a sample size of 59 patients for each group. Therefore, the total sample size will be 120 patients, to be randomized into one of two groups.

Statistical analysis

Statistical analysis was performed using Microsoft® Excel® version 2010 and SPSS® for Windows® version 15.0. Kolmogorov-Smirnov test for normality was applied to the measured variables. Data were described as mean and standard deviation (for parametric variables); median and interquartile range (for non-parametric numeric variables); or number and percentage (for categorical variables). Difference between two independent groups was analyzed using independent student's t-test (for parametric variables); Mann-Whitney's U-test (for non-parametric numeric variables); or chi-squared test (for categorical variables). Clinical efficacy or safety outcomes were expressed in terms of absolute risk reduction (ARR) and the number needed to treat (NNT) or to harm (NNH). Significance level was set at 0.05.

3. Results

A total of 120 women were recruited in the trial. Figure-1 shows study course.

The mean age of all included women was 23.43 ± 2.8 years (range: 19 – 31 years). The mean gestational age was 40.08 ± 1.33 weeks (range: 37.29 – 41.71 weeks). The mean body mass index (BMI) was 27.08 ± 3.26 Kg/m^2 (range: 24.29 – 37.71 Kg/m^2). There were no significant difference between both groups regarding age, gestational age and BMI. The median initial Bishop score in all included women was 7 (range: 6 – 9; interquartile range: 7 – 8). There was no significant difference between both groups regarding initial Bishop score. Indications for induction of labor are shown in table-1.

Table-1 Indications of Induction of Labor in Included Women

Indication for Induction of Labor	
Postdate (≥ 41 weeks' gestation)	103 (85.8%)
Hypertensive Disorders	8 (6.7%)
Diabetes Mellitus	7 (5.8%)
Oligohydramnios	2 (1.7%)

Data presented as number (percentage).

Of the included 60 women of group II [Delayed Oxytocin Group], 48 (80%) needed oxytocin infusion, while 12 (20%) did not, in contrast to the 60 women of group I [Immediate Oxytocin Group] who entirely received oxytocin infusion; this difference was statistically significant. The median oxytocin-to-onset of the active phase, oxytocin-to-delivery and onset of the active phase-to-delivery intervals were slightly lower in women of group II [Delayed Oxytocin Group] when compared to women of group I [Immediate Oxytocin Group], but not to a significant level. The median amniotomy-to-onset of the active phase and amniotomy-to-delivery intervals were significantly higher in women of group II when compared to women of group I. The proportion of women who delivered within 12 hours was significantly higher in women of group I when compared to women of group II. Immediate oxytocin

infusion significantly raised the rate of delivery within 12 hours by 23.3% [NNT = 4] (Table-2).

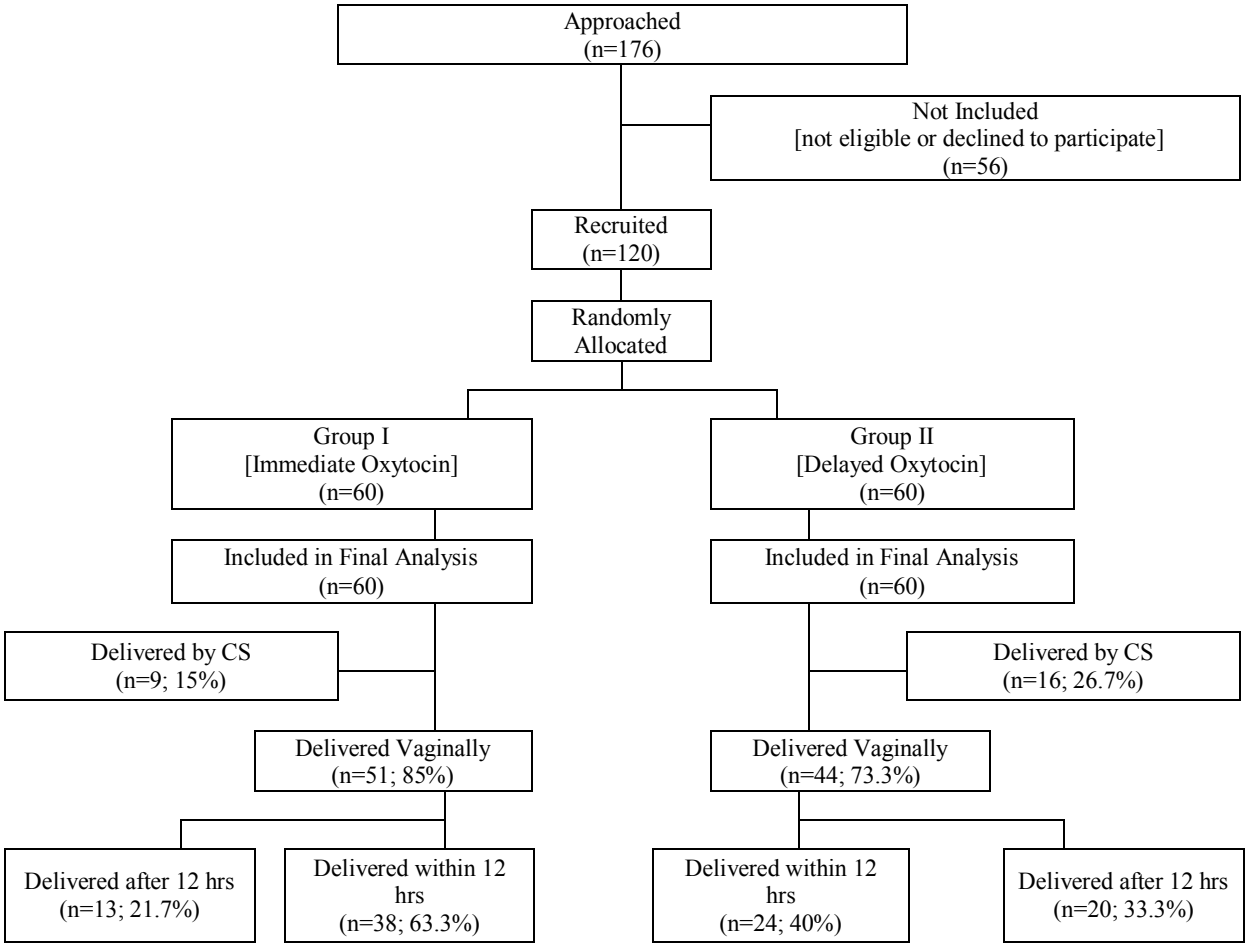

Figure-1. Study Course

Table-2. Difference between Groups regarding Need for Oxytocin Infusion and Duration of Labor

	Group I (Immediate Oxytocin Group)	Group II (Delayed Oxytocin Group)	*P*	ARR	NNT
Need for Oxytocin	60 (100%)	48 (80%)	<0.001*	20%	5
Amniotomy-to-Active Phase Interval	75 (45 – 90)	180 (150 – 210)	<0.001**	-	-
Amniotomy-to-Delivery Interval	360 (330 – 395)	465 (360 – 535)	0.001**	-	-
Oxytocin-to-Active Phase Interval	75 (45 – 90)	60 (35 – 100)	0.270**	-	-
Oxytocin-to-Delivery Interval	360 (330 – 395)	345 (240 – 415)	0.118**	-	-
Active Phase-to-Delivery Interval	290 (245 – 345)	285 (180 – 345)	0.194**	-	-
Delivery within 12 hours	38 (63.3%)	24 (40%)	0.011*	23.3%	4

Data presented as number (percentage); or median (interquartile range)
Intervals are presented in minutes
*Analysis using Chi-Squared Test - **Analysis using Mann-Whitney's U-Test
ARR absolute risk reduction - NNT number needed to treat (approximated to the nearest integer)

The rate of Cesarean section (CS) was higher in women of group II [Delayed Oxytocin Group] when compared to women of group I [Immediate Oxytocin Group], and so were the rates of CS for intrapartum fetal distress and for failed progress of labor. These differences, however, did not reach statistical significance. Immediate, rather than delayed, oxytocin infusion was associated with

reduced risk of CS by 11.7% (NNT = 9), reduced risk of CS for intrapartum fetal distress by 3.3% (NNT = 30), reduced risk of CS for failed progress of labor by 8.3% (NNT = 12), reduced risk of CS for secondary arrest of cervical dilatation by 3.3% (NNT = 30) and reduced risk of CS for failure of descent by 5% (NNT = 20) (Table-3).

Table-3. Difference between Groups regarding Rate and Indications of Cesarean Section

	Group I (Immediate Oxytocin Group) [n=60]	Group II (Delayed Oxytocin Group) [n=60]	*P*	ARR	NNT
Cesarean Section	9 (15%)	16 (26.7%)	0.116	11.7%	9
Intrapartum fetal distress	3 (5%)	5 (8.3%)	0.714	3.3%	30
Failed progress of labor	6 (10%)	11 (18.3%)	0.191	8.3%	12
Arrest of cervical dilatation	4 (6.7%)	6 (10%)	0.509	3.3%	30
Failure of descent	2 (3.3%)	5 (8.3%)	0.436	5%	20

Data presented as number (percentage); Analysis using Continuity-Corrected Chi-Squared Test;
ARR absolute risk reduction; NNT number needed to treat (approximated to the nearest integer)

The median VAS for labor pain was significantly higher in women of group I [Immediate Oxytocin Group] when compared to women of group II [Delayed Oxytocin Group]. The rate of uterine hyperstimulation was slightly higher in women of group I when compared to women of group II. Immediate, rather than delayed, oxytocin infusion was associated with higher risk of uterine hyperstimulation by 1.67% [NNH = 60]. The rates of satisfied women were significantly higher in group I. Immediate, rather than delayed, oxytocin infusion was associated with higher rate of patient satisfaction by 23.3% [NNT = 4] (Table-4).

Table-4 Difference between Groups regarding Labor Pain, Uterine Hyperstimulation and Patient Satisfaction

	Group I (Immediate Oxytocin Group) [n=60]	Group II (Delayed Oxytocin Group) [n=60]	*P*	ARR	NNH /NNT
Labor Pain (10-cm VAS)	8 (7 – 9)	6 (5 – 8)	0.004*	-	-
Uterine Hyperstimulation	2 (3.3%)	1 (1.7%)	0.999**	1.67%	60
Satisfied Women	23 (38.3%)	9 (15%)	0.004**	23.3%	4

Data presented as median (interquartile range); or number (percentage)
* Analysis using Mann-Whitney's U-Test - **Analysis using Continuity-Corrected Chi-Squared Test
ARR absolute risk reduction; NNT number needed to treat – NNH number needed to harm

There were no significant differences between neonates of both groups regarding 1-min and 5-min Apgar scores. There was a similar rate of transient tachypnea of the newborn [TTN] among women of both groups. The rate of neonatal hyperbilirubinemia was slightly higher in group I. Immediate, rather than delayed, oxytocin infusion was associated with higher risk of neonatal hyperbilirubinemia by 3.33% [NNH = 30] (table-5).

Table-5 Difference between Groups regarding Neonatal Outcome

	Group I (Immediate Oxytocin Group)	Group II (Delayed Oxytocin Group)	*P*	ARR	NNH
1-min Apgar Score	6 (6 – 6)	6 (6 – 7)	0.125*	-	-
5-min Apgar Score	8 (7 – 8)	8 (7 – 9)	0.998*	-	-
TTN	1 (1.7%)	1 (1.7%)	1.0**	0	NE
Neonatal Hyperbilirubinemia	5 (8.3%)	3 (5%)	0.714**	3.33%	30

*Analysis using Mann-Whitney's U-Test - ** Analysis using Chi-squared Test; TTN transient tachypnea of the newborn; ARR absolute risk reduction - NNH number needed to harm; NE not estimable due to equality of risk in both groups

4.Discussion

The current trial showed that immediate oxytocin infusion following amniotomy in primiparous women planned for induction of labor was associated with significantly shorter amniotomy-to-delivery interval [mean difference = 54.2 min, 95% CI (21.7 to 130.1)] and significantly higher rates of delivery within 12 hours [NNT = 4]. A significant reduction in the need for oxytocin was the result of delayed oxytocin infusion [20% of women in this group did not need oxytocin, NNT = 9]; and this probably was associated with significant reduction in labor pain perception, slight reduction in uterine hyperstimulation, and slight reduction in rates of neonatal hyperbilirubinemia. The overall women satisfaction, however, significantly went with immediate oxytocin infusion; probably due to the shorter induction interval.

When literature was revised, only one similar randomized clinical trial was found; conducted by Selo-Ojeme *et al.* [7] on 123 primiparous women planned for induction of labor at Barnet and Chase Farm Hospital, London, with comparable initial characteristics (regarding the age, gestational age and the modified Bishop score). The results of the two trials were in agreement in the main outcomes and conclusions, with few discrepancies. The proportion of women who needed oxytocin in the delayed oxytocin group in this study was 80.6%. The proportion of women who delivered vaginally within 12 hours in the immediate oxytocin group was significantly higher than those who received delayed oxytocin [77.1% vs. 58.1%, respectively, p=0.015]. The median amniotomy-to-delivery interval was significantly shorter in those who received immediate oxytocin [8 (4 – 13) hours vs. 10 (7 – 18) hours, respectively, p <0.001]. The rates of uterine hyperstimulation [4.9% vs. 9.7%, respectively, p =0.168] and abnormal CTG [39.3% vs. 29%, respectively, p =0.071] in this latter study, though not significantly different in both groups, were quite high, and, consequently, so were the rates of CS for fetal distress [66.7% vs. 52.9%, respectively]. Nevertheless, the rates of 5-min Apgar score < 7 [3.3% vs. 3.2%], arterial cord pH < 7.2 [3.3% vs. 0%] and NICU admission [3.3% vs. 0%] were very low and disproportionate to those remarkably high rates of uterine hyperstimulation, abnormal CTG and CS for fetal distress. There was probably an over-diagnosis of intrapartum fetal distress in this study.

There was no other published material regarding the appropriate time for starting oxytocin after amniotomy for induction of labor at term. There were, however, numerable randomized clinical trials and even systematic reviews regarding the time of starting oxytocin for induction of labor in women presenting with pre-labor rupture of the membranes (PROM), and in women with dysfunctional labor. The conclusion of the majority of these published materials was that early oxytocin for induction or augmentation significantly reduces the duration of labor without having significant adverse impact on the perinatal outcome [8-11]. Moreover, in a meta-analysis of 9 trials, it was shown that early oxytocin was even associated with significant increase in the rates of spontaneous vaginal delivery [12].

The trial had some points of weakness. Undoubtedly, a sample size of 120 women, though statistically justified, was too small to generalize the results of the current trial or to conclude a guideline for management. In addition, cervical ripening with a prostaglandin analogue agent (misoprostol) should have had an impact on the course of labor in included women. Misoprostol is not just a cervical ripening agent; and is practically known to have a positive impact on uterine contractions [13]. The course and duration of labor, and the maternal and neonatal outcomes, as well, might have been influenced by the pre-induction insertion of this prostaglandin. A third point of weakness was the selected women for recruitment. The majority of women in the trial conducted by Selo-Ojeme et al. and the current one were postdate (≥ 41 weeks). This group of women is heterogeneous; and the perinatal outcome is known to be affected by factors other than the course of labor. This point of weakness was inherent and unavoidable, however. The most common cause for induction of labor was prolonged pregnancy [14]. Cases with possible fetal compromise due to chronic distress (women with abnormal CTG or abnormal fetal growth patterns) were excluded in an attempt to limit the impact of this defect.

In conclusion, early oxytocin infusion, following amniotomy for induction of labor in primiparous women, seems to be advantaged over delayed oxytocin infusion (after 4 hours) by the significantly shorter duration of labor and better women satisfaction, without any significant adverse impact on the maternal and perinatal outcome.

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