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Influence of Preeclampsia on Induction of Labor at Term: A Cohort Study

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Abstract. *Background/Aim: Even though vaginal delivery is a feasible option in patients with preeclampsia, the cesarean section rate in those patients is high. The aim of this study was to evaluate the influence of preeclampsia on induction of labor at term. Patients and Methods: This historical cohort study analyzed inductions of labor in women at term having preeclampsia versus women who were induced due to other reasons. The primary outcome measure was the cesarean section rate. Results: The cesarean section rate was higher in the preeclampsia group for both nulliparous and multiparous women after induction of labor but failed to reach statistical significane. The induction-to-delivery interval was longer in nulliparous women and the rate of vaginal birth within 48 h was lower in the nulliparous patiens with preeclampsia. However, the impact of preeclampsia on the cesarean section rate was not significant in the multivariable analysis following adjustment for BMI and parity. Conclusion: Preeclampsia at term did not influence the cesarean section rate in nulliparous and parous women when labor was induced.*

Worldwide, 10% of all pregnancies are affected by some hypertension-associated complications. Preeclampsia occurs in 2-8% of all pregnancies with a fourfould higher risk of perinatal mortality (1, 2). The only curative treatment for preeclampsia is induced delivery, which is indicated at 37 weeks of gestation at the earliest (3, 4). In cases of severe preeclampsia or if a severe growth restriction is diagnosed, clinicians should consider preterm delivery (4, 5).

The cesaerean section rate in cases of severe preeclampsia is high, in preterm pregnancies up to 70% or even more (6, 7). Even at term, many obstetricians prefer delivery by caesaerean section in women with preeclampsia, although this seems to be associated with a significant postpartum maternal morbidity (6). Since the neonatal outcome is not worsened following induction of labor compared to delivery *via* cesarean section, vaginal delivery is a feasible option (4, 7-9). Therefore, the aim of this study was to evaluate the influence of preeclampsia on labor induction at full-term (37 weeks or more).

Patients and Methods

This historical cohort study was undertaken at a single tertiary perinatal centre between 2011 and 2016. Women with labor induction at term were included. Exclusion criteria were: i) fetal breech position, ii) previous cesarean section, iii) multiple pregnancies, iii) intrauterine fetal death, and iv) structural or chromosomal fetal malformation. Furthermore, patients with premature rupture of membranes were excluded as it is known that it influences the success of labor (10). Patients with preeclampsia were compared to women who underwent induction of labor for other reasons. Preeclampsia was defined as blood pressure ≥140/90 mm Hg combined with either a proteinuria >300 mg total protein within a 24-h urine collection or a ratio of protein to creatinine >30 mg/mmol (4). Ethical approval was given by the institutional review board of our university hospital (247_17 Bc). Informed consent was given by all participants.

Gestational age was determined from the last menstrual period and confirmed by or recalculated with biometric measurements obtained from fetal biometry during early pregnancy (according to current recommendations) (11). Before induction, the Bishop score was assessed by a midwife or a doctor (12). For labor induction, misoprostol (administered orally or vaginally), vaginal dinoproston gel, oxytocin, double-balloon catheter or a combination of these were used. Labor induction was continued until delivery.

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Key Words: Cesarean section, hypertension, induced labor, preeclampsia, term pregnancy.

Table I. *Baseline demographics and pregnancy characteristics.*

Characteristics	Preeclampsia group (n=99)	No preeclampsia group (n=1724)	*p*-Value
Age (years)	31.1±6.2	30.9±5.2	0.6842
Height (cm)	166.8±6.7	167.2±6.7	0.6086
Weight (kg)	91.2±18.4	85.0±17.0	0.0004
Body mass index	31.6±6.5	29.6±5.9	0.0011
Pregnancy	1 (1-7)	1 (1-12)	0.1689
Parity	0 (0-5)	0 (0-5)	0.0146
Gestational age (days)	272.5±8.3	283.8±8.0	<0.0001
Birth weight (grams)	3,197.5±483.7	3,492.9±499.6	<0.0001
Bishop score	1 (0-10)	2 (0-10)	0.0088
Fetal growth restriction	10 (10.1%)	104 (6.0%)	0.1040
Placental insufficiency, abnormal doppler (n, %)	0	22 (1.3%)	0.6283
Gestational diabetes (n, %)	14 (14.1%)	258 (15.0%)	0.8230
Intrahepatic cholestasis of pregnancy (n, %)	1 (1.0%)	23 (1.3%)	1.0000
Method of induction of labour (first choice)			
Double-balloon catheter	49 (49.5%)	903 (52.4%)	0.5725
Dinoproston (PGE 2)	19 (19.2%)	160 (9.3%)	0.0013
Misoprostol (PGE 1)	31 (31.3%)	646 (37.5%)	0.2160
Oxytocin	0	14 (0.8%)	1.0000

Quantitative data are presented as mean with standard deviation or as median (range) values. For qualitative factors, absolute and relative frequencies are given. $p<0.05$ was considered significant.

Table II. *Outcome parameters.*

Outcome parameters	Preeclampsia group (n=99)	No preeclampsia group (n=1724)	*p*-Value
Mode of delivery (n, %)			
Normal vaginal delivery	60 (60.6%)	1,167 (67.7%)	0.1439
Surgical vaginal delivery	7 (7.1%)	175 (10.2%)	0.3201
Cesarean section	32 (32.3%)	382 (22.2%)	0.0189
Induction-Delivery-Interval (min)*	1,912 (255-4,237)	1,575 (97-4,318)	0.0051
Vaginal delivery within 24 h (n, %)**	15 (24.6%)	504 (31.1%)	0.0226
Vaginal delivery within 48 h (n, %)**	41 (67.2%)	1070 (83.1%)	0.0015
Failed induction (no delivery within 72 h; n, %)**	4 (6.6%)	68 (5.3%)	0.5625
Arterial umbilical pH	7.278±0.078	7.280±0.080	0.7793
Arterial umbilical pH <7.05 (n, %)	0	8 (0.5%)	1.0000
Arterial umbilical pH <7.10 (n, %)	2 (2.0%)	23 (1.3%)	0.6430
BE <–12 (n, %)	1 (1.0%)	30 (1.7%)	1.0000
Apgar score at 5 min <7 (n, %)	2 (2.0%)	21 (1.2%)	0.3587
BE <–12 and Apgar score at 5 min <7 (n, %)	0	4 (0.2%)	1.0000
Abnormal CTG (n, %)	17 (17.2%)	306 (17.7%)	0.8836
Fetal blood analysis (n, %)	3 (3.0%)	40 (2.3%)	0.5047
Epidural anaesthesia (n, %)	37 (37.4%)	799 (46.5%)	0.0762
Oxytocin (n, %)	64 (65.3%)	717 (42.3%)	0.1403
Meconium-stained amniotic liquor (n, %)	17 (17.2%)	304 (17.6%)	0.9066
Chorioamnionitis (n, %)	1 (1.0%)	10 (0.6%)	0.4599
Postpartum transfer to neonatal care unit, total (n, %)	23 (23.2%)	268 (15.6%)	0.0423
Infection of the newborn (n, %)	4 (4.0%)	85 (5.1%)	0.8149

BE: Base excess; h: hours; CTG: cardiotocogram. *Cesarean sections and failed induction of labor are excluded. **Cesarean sections are excluded.

The primary outcome measure was the cesarean section rate. Secondary outcome measures included i) the induction-to-delivery interval, ii) the rate of vaginal deliveries within 24 and 48 h, iii) a failed labor induction (defined as no vaginal delivery within 72 h), iv) neonatal outcome parameters, such as arterial umbilical cord pH and base excess, Apgar score after 5 min, and postpartum admission to neonatal care unit, and v) maternal outcome parameter (chorioamnionitis).

All statistical calculations were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). For quantitative variables that were approximately following a normal distribution we calculated the mean value and standard deviation. For skewed, ordinal or quantitative discrete data we provide the median value together with minimum and maximum. Qualitative factors are presented by relative and absolute frequencies. Two mean values were compared using a 2-sample *t*-test. For data that is not normally distributed we used the Mann Whitney *U*-test instead. For qualitative factors Chi2-test or Fisher's exact test were performed, as appropriate.

Furthermore, we performed a multivariable logistic regression analysis for the primary outcome measure "cesarean section rate" in order to analyse several variables simultaneously using the "forward selection" method. This technique enabled us to adjust for differences in baseline characteristics and potential confounders.

In general, the result of a statistical test was considered as significant if the *p*-Value was less than 0.05.

Results

In the investigated period there were 14,072 deliveries. Labor was induced in 3,148 women (22.4%). After consideration of the inclusion and exclusion criteria, 1,823 cases were included in this study. There were 99 labor inductions for preeclampsia and 1,724 for other indications.

The demographic parameters are given in Table I. In the preeclampsia group, patients had a higher weight (91.2±18.4 kg *vs.* 85.0±17.0 kg, $p=0.0004$), as well as a higher a resulting body mass index (BMI in kg/m^2) (31.6±6.5 *vs.*

Table III. *Outcome parameters in nulliparous and parous women.*

Outcome parameters	Nulliparous			Parous		
	Preeclampsia group (n=75)	No preeclampsia group (n=1088)	*p*-Value	Preeclampsia group (n=24)	No preeclampsia group (n=636)	*p*-Value
Mode of delivery (n, %)						
Normal vaginal delivery	40 (53.3%)	588 (54.0%)	0.9049	20 (83%)	579 (91.0%)	0.2664
Surgical vaginal delivery	7 (9.3%)	155 (14.2%)	0.2346	0	20 (3.1%)	1.0000
Cesarean section	28 (37.3%)	345 (31.7%)	0.3129	4 (16.7%)	37 (5.8%)	0.0550
Induction-Delivery-Interval (min)*	2,261 (582-4,237)	1,767 (288-4,318)	0.0111	1,464 (255-3,713)	1,307 (97-4,203)	0.3426
Vaginal delivery within 24 h (n, %)**	8 (19.0%)	203 (28.4%)	0.1893	7 (36.8%)	301 (52.5%)	0.1781
Vaginal delivery within 48 h (n, %)**	24 (57.1%)	571 (79.9%)	0.0005	17 (89.5%)	499 (87.1%)	1.0000
Failed induction (no delivery within 72 h; n, %)**	4 (9.5%)	47 (6.6%)	0.5186	0	21 (3.7%)	1.0000
Arterial umbilical pH	7.268±0.074	7.276±0.081	0.3649	7.311±0.082	7.287±0.077	0.1462
Arterial umbilical pH <7.05 (n, %)	0	7 (0.6%)	1.0000	0	1 (0.2%)	1.0000
Arterial umbilical pH <7.10 (n, %)	1 (1.3%)	20 (1.8%)	1.0000	1 (4.2%)	3 (0.5%)	0.1380
BE <–12 (n, %)	1 (1.3%)	21 (1.9%)	1.0000	0	9 (1.4%)	1.0000
Apgar score at 5 min <7 (n, %)	2 (2.7%)	20 (1.8%)	0.6485	0	1 (0.2%)	1.0000
BE <–12 and Apgar score at 5 min <7 (n, %)	0	4 (0.4%)	1.0000	0	0	n. c.
Abnormal CTG (n, %)	16 (21.3%)	251 (23.1%)	0.7294	1 (4.2%)	55 (8.6%)	0.7123
Fetal blood analysis (n, %)	3 (4.0%)	39 (3.6%)	0.7486	0	1 (0.2%)	1.0000
Epidural anaesthesia (n, %)	33 (44.0%)	654 (60.4%)	0.0050	4 (16.7%)	145 (22.8%)	0.4806
Oxytocin (n, %)	31 (41.9%)	595 (55.9%)	0.0195	3 (12.5%)	122 (19.3%)	0.5966
Meconium-stained amniotic liquor (n, %)	14 (18.7%)	237 (21.8%)	0.5257	3 12.5%)	67 (10.5%)	0.7332
Chorioamnionitis (n, %)	1 (1.3%)	10 (0.9%)	0.5212	0	0	n. c.
care unit, total (n, %)						
Postpartum transfer to neonatal	19 (25.3%)	201 (18.5%)	0.1424	4 (16.7%)	67 (10.5%)	0.3141
Infection of the newborn (n, %)	4 (5.3%)	69 (6.3%)	1.0000	0	18 (2.8$)	1.0000

BE: Base excess; n.c.: not calculable. $p<0.05$ was considered significant. *Cesarean sections and failed induction of labor are excluded. **Cesarean sections are excluded.

29.6±5.9, $p=0.0011$) compared to the "no preeclampsia" group. Furthermore, labor was induced earlier (272.5±8.3 days of gestation *vs*. 283.8±8.0 days of gestation, $p<0.0001$) and birth weight was lower (3197.5±483.7 grams *vs*. 3392.9±499.6 grams, $p<0.0001$) in the preeclampsia group. The Bishop score in the preeclampsia group was lower [median=1 (0-1) *vs*. median=2 (0-10), $p=0.0088$]. The proportions relating to the methods for induction of labor were similar except for dinoproston use where a higher rate has been observed in the preeclampsia group (19.2% *vs*. 9.3%, $p=0.0013$). The majority of patients in the control group was induced because of pregnancy at or beyond 41 weeks of gestation (52.6%), followed by induction on request (12.4%) and gestational diabetes (8.2%).

The pooled outcome parameters are given in Table II. The cesarean section rate, which was the primary outcome measure, was significantly higher in the preeclampsia group (32.3% *vs*. 22.2%, $p=0.0189$). Moreover, in the preeclampsia group, the induction-to-delivery interval was longer [median 1912 (255-4237) *vs*. 1575 (97-4318) min, $p=0.0051$] and the vaginal birth rates within 24 h (24.6% *vs*. 31.1%, $p=0.0226$) and 48 h (67.2% *vs*. 83.1%, $p=0.0015$) were lower. Newborns had to be transferred to the neonatal care unit more often when labor was induced for preeclampsia (23.2% *vs*. 15.6%, $p=0.0423$).

The outcome parameters according to parity are demonstrated in Table III. When considering the parity, the cesarean section rate was not significantly different in nulliparous (37.3% *vs*. 31.7%, $p=0.3129$) between women with and without preclampsia; in parous women, however, the difference between these two groups (16.7% *vs*. 5.8%, $p=0.0550$) just barely failed to reach significance.

In nulliparous women, the induction-to-delivery interval was longer in the preeclampsia group [2261 (582-4237) *vs*. 1767 (288-4318) min, $p=0.0111$), and the rate of vaginal deliveries within 48 h (57.1% *vs*. 79.9%, $p=0.0005$) was lower. Oxytocin was administered more often when there was no preeclampsia present (41.9% *vs*. 55.9%, $p=0.0195$). The epidural anaesthesia rate was lower in women with preeclampsia (44.0% *vs*. 60.4%, $p=0.0050$).

Table IV. *Univariable and multiple Logistic regression analysis of the primary outcome measure cesarean section rate.*

	Univariable analysis Odds ratio	Univariable analysis (*p*-Value)	Multiple analysis Odds ratio	Multiple analysis significant *p*-Value
Preeclampsia	1.679	0.0199		
Body mass index (kg/m^2)	1.063	<0.0001	1.066	<0.0001
Age (years)	1.018	0.1013		
Parity	0.248	<0.0001	0.263	<0.0001
Gestational age (days)	1.008	0.2248		
Birth weight (kg)	1.114	0.3347		
Bishop score	0.811	<0.0001	0.893	0.0036
(Gestational) diabetes	1.302	0.0786		
Fetal growth restriction	0.902	0.6628		
Indication for induction of labour				
Pregnancy at or beyond 41 weeks	1.016	0.8889		
Gestational diabetes	0.999	0.9965		
On request	0.733	0.0967		
Anhydramnios/Oligohydramnios	0.718	0.1914		
Suspected fetal macrosomia	2.307	0.0266	2.888	0.0162
Less fetal movements	0.850	0.8850		
Fetal growth restriction; placental insufficiency; abnormal Doppler	0.644	0.0668		
Preeclampsia, hypertensive disorders	1.751	0.0016		
Abnormal CTG	0.972	0.9518		
Intrahepatic cholestasis in pregnancy	0.321	0.1257		
Other	1.471	0.1572		

Ctg: Cardiotocogram, kg: kilogram.

In parous women, no statistically significant differences between the preeclampsia group and the control group could be found.

The results of logistic regression analysis for the outcome measures "cesarean section" are shown in Table IV. In the multiple model, BMI, parity, and Bishop score remained significant. High BMI increased the cesarean section rate whereas high parity and high Bishop score decreased it. Concerning the indication for induction of labor, only a suspected fetal macrosomia was relevant and increased the cesarean section rate. Remarkably, the presence of preeclampsia is not significantly associated with the cesarean section rate. This finding suggests that preeclampsia does not affect causally the outcome. The significant test result in the univariable analysis (p=0.0189, Table II) is due to different baseline characeristics. According to the p-Values resulting from the multiple logistic regression analysis, high BMI and low parity (not preeclampsia) seem to be the most important risk factors for cesarean section.

Discussion

This study compared the induction of labor for preeclampsia with labor inductions for other reasons. The analysis of data (especially the multiple regression analysis) could demonstrate that induction of labor for preeclampsia is not associated with a higher cesarean section rate but with a longer induction-to-delivery interval and less births within 48 h after induction in nulliparous women.

Induction of labor is more frequent in women with preeclampsia and eclampsia (2). Success of induction depends on gestational age and is reported to be higher in pregnancies after 32 weeks of gestation (7). It has been demonstrated that after 32 weeks of gestation the vaginal delivery rate after induction of labor ranges around 62.5-68.8% in patients with preeclampsia (6-8, 13).

In the present study, we could not find a higher cesarean section rate following induction of labor for preeclampsia after having adjusted for BMI and parity. These results confirm the findings of Bernardes *et al.* who has shown that induction of labor is not associated with increased rates of cesarean section or adverse neonatal outcome in pregnancies between 36 and 41 weeks of gestation with gestational hypertension or mild preeclampsia compared to expectative management, even in patients with an unripe cervix (Bishop score<6) (14). In contrast to these findings, in another retrospective analysis nulliparous and parous women had higher cesarean section rates compared to women without preeclampsia (30% *vs.* 23%, p=0.011) (15). These results could be explained by inclusion of patients in early weeks of gestation as the success of vaginal delivery is described to be lower at those stages (7). In contrast to our results,

Thrornton *et al*. have shown in a retrospective analysis that induction of labor (rather than spontaneous labor) in women with preeclampsia or superimposed preeclampsia leads to lower rates of vaginal delivery than spontaneous labor compared to women without a hypertensive disorder during pregnancy (16).

Induction of labor was not associated with an increase in neonatal morbidity or mortality (7). It has been shown that induction of labor is associated with decreased risks of neonatal complications (any of the following three: i) 5-min Apgar score less than 5, ii) arterial cord pH less than 7.0, or iii) the clinical diagnoses of asphyxia or hypoxic–ischemic encephalopathy), NICU admission and respiratory distress syndrome compared to planned cesarean delivery in patients with mild, severe or superimposed preeclampsia >34+0 weeks of gestation. Furthermore, induction of labor has not been associated with an increased risk of the maternal outcome parameters (hysterectomy, transfusion, ICU admission, deep venous thrombosis, and pulmonary embolism) compared to planned cesarean delivery (13).

In our study we could not demonstrate a significant difference in the maternal outcome parameters following induction of labor in women with preeclampsia. Interestingly, it has been previously demonstrated that women with preeclampsia having a cesarean section have a significantly higher severe maternal morbidity rate following caeserean section (54.0 *vs*. 32.7%) (6). A randomized controlled trial with women between 36+0 and 41+0 weeks of gestation with gestational hypertension or mild preeclampsia has also demonstrated that induction of labor is associated with an improved maternal outcome compared to expectative management, without increasing the cesarean section rate (3). These results mentioned above are in line with our findings as we could not find any differences concerning maternal and fetal outcome parameters in women with preeclampsia who´s labor was induced in comparison to labor induction because of other indications.

This study has some limitations and some strengths. The main limitation is its retrospective nature of data collection. Furthermore, the two groups differed significantly from one another with regard to certain factors. Women in the preeclampsia group had a higher weight, BMI and gestational age as well as a lower Bishop score and birth weight. These factors, especially high BMI and low Bishop score, are well known to be risk factors for failed induction. However, the impact of these factors has been controlled by a multivariable analysis. Since there was no difference regarding the cesarean section rate between the two groups when stratifiying for parity and BMI, the safety of labor induction in preeclamptic women can be underlined. The stratification for parity is a main strength of this investigation. In most of the previous investigations, there was no stratification for parity which may result in counterfactual conclusions. When only considering our pooled data, one might conclude that there was a different cesarean section rate between the two groups.

In conclusion, labor induction in patients with preeclampsia did not influence the cesarean section rate in nulliparous and parous women at term.

Conflicts of Interest

No conflicts of interest to declare.

Authors' Contributions

JP contributed to acquisition of data and was a major contributor in writing the article. CW contributed analysis and interpretation of data. UD and FS contributetd to aquisition of data and were involved in revising the article critically. FF involved in revising the article critically. MWB revised the article critically and gave final approval of the version to be published. SK contributed to aquisition of data, conception and design and gave final approval of the version to be published. All Authors read and approved the final article.

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