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Research Article

INDUCTION OF LABOR BY PROSTAGLANDIN: A REVIEW FOR INDICATIONS AND RISK FOR CESAREAN SECTION

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ABSTRACT

Objective: Labor induction by medication is now preferred by many obstetricians. The impact of induction remains ambiguous, although many studies and systematic reviews have been conducted. Few studies have reported for its better outcomes while other studies with poor outcomes. The objective of the study is to identify the common indications of induction and the risk of cesarean section after induction.

Methods: Various standardized databases, such as Pub Med, Scopus, and Google Scholar, were used to collect the scientific studies, where prostaglandin was used as drug of choice for induction of labor. The key words used were induction of labor, indications of induction, induction by misoprostol, induction and risk of cesarean section, etc. The survey spans over 22 years of study articles published from the year 1995-2017.

Result: A total of 112 studies have been included to analyze the indications and risk of cesarean section. The most common indication found in most of the studies was post-term pregnancy. The risk of cesarean section varied from 3% to 48.7%. The common reasons for which the cesarean section was planned were, failed induction, nonprogress of labor, fetal distress, and undiagnosed CPD.

Conclusion: Most of the studies recommend induction of labor as a safer option with lower risk of c-section.

Keywords: Induction of labor, Indication of induction, Induction and c-section, Predictors of successful induction.

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INTRODUCTION

The labor is a unique experience for the mother and she anxiously waits for the labor pain to come naturally. But when this fails to happen, she undergoes a procedure that artificially initiates the labor which is called induction of labor. The familiarity of the procedure is slowly rising in every setting from rural to well-equipped urban hospital. There is a demand in reducing the rate of unnecessary cesarean section and improvement of fetal outcomes. This is considered when delivery is thought to be the safer option than continuing the pregnancy [1]. Prostaglandins are lipids, found in cervical fluid, and decidua that reduce the inflammatory process and dilate the cervix [2,3]. Prostaglandine and its group of drugs when used for ripening of cervix in case of favorable or unfavorable cervix, was effective in bringing cervical favorability and with good progress of labor by successful induction with vaginal delivery within 24 hrs without much operative delivery [4-7]. The reasons for considering induction are many and vary from obstetrician to obstetrician and from country to country [8]. The most common indication that requires induction of labor is postdated pregnancy [9-22]. Another frequently cited indication is term premature rupture of membrane [12,13,23,24]. Nevertheless, the hypertensive disorder remains a rare indication, rather this requires induction in higher rate [14,20,21,25,26]. The less frequent indications are oligohydramnios, IUGR, gestational diabetes, fetal distress, macrosomia, fetal death, decreased fetal movement, uncomplicated twins, polyhydramnios, Rh isoimmunization, chorioamnionitis, heart disease, and other fetal indications [9-14]. In a meta-analysis, it is also observed that the common indications cited by many researchers are post-term pregnancy, PROM, oligohydramnios, twins, macrosomia, pre-eclampsia, diabetes, and IUGR [23]. The outcomes of induction of labor are comparatively better than the spontaneous labor as reviewed from certain studies, while other studies found higher adverse outcomes associated with induction than the spontaneous labor. The causes for failure are mostly failed induction, fetal distress, undiagnosed CPD, meconeum stained liquor, nonprogress of labor, and prolonged latent phase [10-13,27,28].

METHODS

To collect a good number of quality studies with best recommendations, many electronic data bases were searched. The literature was collected from databases such as Pubmed, Scopus, Science Direct, and Google Scholar. The search was based on the keywords such as induction of labor, indication of induction, failed induction, induction in post-term pregnancy, induction in PROM, induction and risk of cesarean section and others. The literature was searched from the year 1995 onward. The literatures mostly included the studies which were systematic reviews, meta-analysis, randomized controlled trial (RCT), and cohort with strong recommendations. The indication of induction was studied from all kinds of scientific literatures those have specifically mentioned the indications. The studies on elective induction and studies on other methods of induction were excluded from the search.

RESULT

The literature was compiled in an ascending order, and a total of 22 articles were analyzed for tabulating the indications for induction of labor. Table 1 shows the most frequent indications of induction in percentage.

The most common indication found by many authors is postdated pregnancy. Pregnancy when continues beyond 40 weeks is post-term pregnancy. About 7% of all pregnancies are post-term pregnancy [39]. Dean Leduce and Jarson Gardosi recorded postdates as highest indication for induction of labor [16,40]. Similarly, frequent indication for induction was postdates observed by Guerra *et al.* [10,26,41] Along with postdates, the hypertensive diseases of pregnancy are many times become the main indications for induction of labor [21]. Whereas

Table 1: Indications of induction of labor

Author	Year	Postdates	Term PROM	Oligohydramnios	Hypertensive disorder	IUFD	IUGR	GDM	Uncomplicated twins	Macrosomia	Decreased fetal movement	Iso-immunization	Maternal request	Fetal death	Others
Ekele *et al.* [21]	2007	40	10		38	10									2
Sanchez-Ramos *et al.* [29]	2003	80	14		8										6
Bueno *et al.* [18]	2005	54.6	5.6	6.1	1.5		9.2	5.1		3.1					14.8
Boulvain *et al.* [30]	2008	38			36			13							13
Mealing *et al.* [9]	2009	33.4	11		13.1	0.8	4.1	4.4				0.2		0.6	32.5
Rayamajhi *et al.* [31]	2009	51.28	17.31	8.97	8.33						7.69				
Admani [10]	2010	32													
Esiromo [11]	2012	50	8.4	16											8.5
Shah and Doshi [32]	2013	29.72	15.09	1.89	28.77									8.49	10.84
Verhoeven *et al.* [22]	2013	20	4	18		3	6						20		21
Khireddine *et al.* [17]	2013	76	12	8											
Lawani *et al.* [13]	2014	45.8	31.9		4.7	12.4	0.4	0.4							0.25
Chirwa [25]	2014	12.6	15		69.3										
Lamichhane *et al.* [12]	2016	44.5	21.3	11.5	12	1.02		1.79			3.8				
Tripathy *et al.* [33]	2016	26	15	27.5	3.5										
Bello and Akinyotu [24]	2016	25	26		13.5		3.8	2.9						18.3	8.9
Laddad *et al.* [34]	2013	28		2.5	37	7.5	7								17.5
Vogel *et al.* [35]	2013	14.8	27.3		8.2	18.8	2.2		2.7		1.6				
Soni *et al.* [36]	2017	10.8	39.8	1.56	15.4		8.54	1.35	1.14			0.72			
Guerra *et al.* [26]	2009	8.8	25.3		7.5	6	3.3		2.1					2.8	20.3
Tolcher *et al.* [37]	2015	36.9	13.5	8.6	12.6	2.8	3.2	9							5.4
Heimstad *et al.* [38]	2007	73													

Chirwa found all three, hypertension (69.3%), PROM (15.0%), and postdated (12.6%) as common indications. Similarly, Sanchez-Ramos *et al*. observed 80% of indications for post-term pregnancies and rest for pregnancy induced hypertension and PROM [42]. Mozurkewich *et al*. and Abdul and Guerra *et al*. reported both postdated and PROM are the common indications for induction with high-quality evidence from various studies, whereas oligohydramnios was found with moderate evidence [26,43]. The induction of labor is commonly indicated in prevention of prolonged pregnancy, prelabor rupture of membranes after 34 weeks, intrauterine fetal death, placental abruption, chorioamnionitis, and hypertensive disorders as stated by NICE and ACOG [44,45]. Folasade and Oriyomi also recorded 25% of indications for postdates and 26% for premature rupture of labor [24]. Lawani *et al.* found the major indications as postdates (45.8%), term PROM (31.9%), pre-eclampsia (4.7%), and preterm PROM (3.7%) [13]. The common causes for which the induction were carried out in the United States were pre-eclampsia and postdates pregnancies and in few cases the premature rupture of membrane [46]. When the pregnancy over 41 weeks is induced, it is associated with fewer cesarean sections compared to expectant treatment [47]. Similarly, Mishanina *et al*. reported that the postdates pregnancy is associated with a reduced risk of cesarean delivery [48]. When labor was induced in term PROM, the rate of cesarean section remained almost same as the compared group [32]. However, the induction in pre-eclamptic group, studied by Xenakis *et al*. shows higher rate of cesarean section (Table 2) [49].

The data reviewed gives a conflicting picture that there is a trends toward decreased cesarean section with good cervical dilatation after misoprostol administration and the same time it is evident that there is an increased cesarean delivery for fetal distress and undiagnosed CPD. Many studies revealed that the prostaglandin and its group of drugs when used for ripening of cervix in case of favorable or unfavorable cervix, was effective in bringing cervical favorability, good progress of labor with a successful vaginal delivery within 24 hrs [34].

The rate of cesarean section was lowered by induction has been reported in many research studies. The successful vaginal delivery after induction was 70% [69], 75% [70], 89.1% [6]. Bueno *et al*. found that the vaginal delivery occurred in 73.5% of women in the induction group, and the rate of cesarean delivery was 26.5% [18]. Sahanaz *et al*. reported vaginal delivery of 78.9% and 21.1% of cesarean section after induction of labor [56,71]. However, Admani found in her study the success rate of 50% with similar rate of failure. The similar rate was observed in the study of Pravati *et al*. [33]. Bello and Akinyotu found induction failed with cesarean section in about 36.5% of women. Boulvain *et al*. demonstrated higher cesarean section with adverse perinatal outcomes after induction of labor [30]. Induced women had significantly higher cesarean rate than the spontaneous group [5,72]. However, Boulvain *et al*. did not get any clear risk of c-section after induction [73]. Sometime it was observed that there are no significant differences in CS rates between the groups of vaginal misoprostol or dinoprostone after induction [74]. In other instances, there is significant difference and it was found in CS rate between in the induction group and the spontaneous group both in nulliparous women (25.3% vs. 8.6%, $p<0.001$) and multiparous women (3.8% vs. 0.3%, $p=0.002$) [10]. Similarly, the induction is associated with a significant increase in the risk of C-section than those who delivered spontaneously [59]. Boulvain *et al*. demonstrated higher cesarean section with adverse perinatal outcomes after induction of labor [30]. Clader reported little higher (28%) rate of cesarean section than the vaginal delivery (11%) after induction of labor with misoprostol [75]. However, many studies reported higher rate of vaginal delivery after induction (70% [69], 75% [70], 89.1% [6]). The success rate for vaginal delivery was 70% and this rate varied little in accordance with the country or the method used [58] Alfirevic *et al*. study revealed that though the vaginal prostaglandins increase the chance of uterine hyperstimulation but this increase the likelihood of vaginal birth within 24 hrs [76]. Whereas other studies shows the risk of cesarean delivery was 12% lower with labor induction than with expectant management (pooled relative

Table 2: The rate and causes of cesarean section after induction and its' predicting factors

Author	Year	Rate of c-section (%)	Causes of cesarean section	Predictors of cesarean section
Chirwa [25]	2014	17	Failed induction, fetal distress, CPD	No misoprostol
Tolcher *et al*. [37]	2015	29.4	Nonreassuring heart rate	Advanced age, short height, greater BMI, weight gain, hypertension, diabetes mellitus and initial cervical dilation <3 cm
Verhoeven *et al*. [22]	2013	3	Failure to progress and fetal distress	History of preterm birth, maternal height and initial dilatation
Bueno *et al*. [18]	2007	26.5	Induction failure, nonreassuring fetal monitoring, pelvic disproportion, failure to progress	Cervical length, Bishop score and parity
Admani [10]	2014	32	Fetal distress, failed induction, nonprogress of labor and meconium stained liquor	Favorable Bishop score and average-sized infants
Lee *et al*. [50]	2015	25.3	Induction failure	Maternal age, BMI, Bishop score and parity
Park [51]	2007	14	Previous obstetric history, previous mid-trimester loss and preterm delivery	Earlier gestational age, previous obstetric history, and preterm delivery
Soni *et al.* [36]	2017	30.3	Failed induction, fetal distress, nonprogress of labor and undiagnosed CPD, malposition	
Ezechi *et al*. [28]	2004	27.92	Cephalopelvic disproportion, fetal distress, prolong labor, and antepartum hemorrhage	
Lawani *et al.* [13]	2014	24.1	Fetal distress, Prolonged labor, Cephalopelvic disproportion fetal distress, prolonged labor and cord prolapse	
Jayaprakash *et al*. [52]	2016	8	Failed induction and fetal distress	
Bello and Akinyotu [24]	2014	36.5		Higher parity, later gestation and misoprostol ripening
Khan *et al.* [27]	2015	18.1		Nulliparity, poor Bishop score and prolonged latent phage
Girma *et al.* [53]	2016	10.7		Bishop score, timing of induction and neonatal weight
Marroquin *et al*. [54]	2013	48.7		Younger age, lower BMI and lower maternal weight
Danielsen *et al.* [55]	2016	28.5		Bishop score, non-reassuring fetal status, failure to descend, malpresentation, abruption and worsening maternal medical status
Ahmadi *et al*. [56]	2016	21.1		Bishop score, parity and gestational age
Parkes *et al.* [57]	2016	17.1		Intrauterine growth restriction, oligohydramnios, placental abruption, macrosomia and post-term pregnancy
Vahratian *et al.* [58]	2005	30		Unfavorable cervix
Davey and King [59]	2016	26.5		Use of analgesia, higher birth weight, older maternal age
Laughon *et al.* [60]	2011			Bishop score
Teixeira *et al.* [61]	2012			Bishop score
Mbele *et al*. [20]	2007			Primigravidity
Hurissa *et al.* [62]	2015			Advanced age, primiparity, unfavorable bishop score, premature rupture of membrane, greater for gestation and bad obstetric history
Hatfield *et al.* [15]	2007			Bishop score and parity
Grobman [63]	2015			Bishop score and parity
Crane [64]	2006			Maternal age, weight, height, BMI, gestational age, birth weight and amniotic fluid index
Ennen *et al*. [65]	2009			Drug doses and cervical dilatation
Pevnzer *et al*. [66]	2009			Drug doses and cervical dilatation
Ehrenthal *et al*. [67]	2010			Drug doses and cervical dilatation
Glantz [68]	2010			Drug doses and cervical dilatation

BMI: Body mass index

risk [RR] 0.88, 95% confidence interval [CI] 0.84-0.93; I^2=0%) [48]. Wennerholm *et al*. also confirmed higher c-section by expectant management rather in the induction method [77]. The cesarean delivery rate in the induction group was 36.5% compared to 34.4% in the expectant management group [78]. Women undergoing induction of labor at 39 weeks without an acute obstetric medical indication were more likely to deliver vaginally than those managed expectantly [79]. Caughey found whether it is 37 or 39, there is no difference in cesarean section but at 40 and 41 weeks of gestation the women had a lower risk of cesarean delivery [80].

The reason of cesarean section is described by Pravati *et al*. as poor progress, fetal distress, cephalo-pelvic disproportion, oligohydramnios, and meconium staining [33]. Dr. Rashida found the reasons for cesarean

as failed induction (52%), fetal distress (23%), and CPD (18%) [10]. Ezechi *et al*. reported the reasons for failed induction with misoprostol include cephalopelvic disproportion, fetal distress, prolong labor, and antepartum hemorrhage [28] Lawani *et al*. also described about fetal distress, prolonged labor, cephalopelvic disproportion as reasons for cesarean section [13]. From the study of Bueno *et al*., it is understood that the major reasons for cesarean delivery are induction failure (34%), nonreassuring fetal monitoring (28.9%), pelvic disproportion (17%), and failure to progress (14.9%) [18].

The major predicting factor for a successful vaginal delivery after induction is the cervical factor [20,43,52,55,60,61,81,82]. Teixeira *et al*. found in their meta-analysis, the Bishop score as greater determinant of successful induction [61]. Danielsen *et al*. stressed that a Bishop score of more than seven should be considered before induction as Bishop score is very good predictor of successful induction [55]. Vrouenraets *et al*. reported that a Bishop score of 5 or less is a significant risk factor for a cesarean delivery [83] Selo-Ojeme *et al*. viewed that regardless of membrane status, the CS rates were high in unfavorable cervix after induction of labor [84]. Dean Leduc highlighted that induction of labor among women with poor cervical dilatation is associated with higher rate of cesarean section [16]. Bello and Akinyotu found the predicting factors for risk of cesarean section are higher parity, later gestation and misoprostol ripening. Lee *et al*. observed the association of the higher CS rate with lower Bishop score, advanced maternal age, nulliparity and higher body mass index (BMI). Rashida reported the success rate induction with vaginal delivery that increased with increase of age. Rebecca Dekker found interestingly the rate is rising by age that is 29.5% in age 25-29 years to 33.0% in 30-34 years and 38.5% in 35-39 years and so on [85]. Rayamajhi *et al*. also noticed failure rate of 53.8% with advanced maternal age >30 years [31]. Gerli *et al*. also viewed that age is directly related to risk of cesarean section after a induction [86]. Hurissa *et al*. reported about the risk of cesarean section in association with advanced age, primiparity, unfavorable bishop score, later gestation, PROM, and bad obstetric history. The success was again related independently to cervical factors and parity [18]. Hatfield *et al*., Grobman, Tolcher *et al*. found older maternal age, shorter maternal height, greater BMI, greater weight gain during pregnancy, older gestational age, hypertension, diabetes mellitus, and initial cervical dilation as independent risk factors for increased risk of cesarean delivery [37,62,63]. Similarly, Crane reported the predictive factors as maternal age, weight, height, BMI, ethnicity, and socioeconomic status. Whereas Park found a single factor that is gestational age as a predictor of successful labor. Sometime the failed induction was dependent on drug doses and cervical dilatation [65-68]. Dublins reported increased cesarean delivery was associated with nulliparous rather than multiparous women with increased risk of instrumental delivery and shoulder dystocia [19]. Admani found higher rate of vaginal delivery in multipara than primipara. Lisa revealed that both the nulliparas (27%) and multiparas (13%) had an increased cesarean rate compared to spontaneous labor [87]. Compared to spontaneous onset of delivery, induction of labor is associated with an increased risk for emergency cesarean section among nulliparous and multiparous women [88] Alicia ault cited that the major risk associated with a failed induction at 39 weeks is cesarean delivery [89]. Park reported earlier gestational age as a significant predictive factor for failed IOL [51]. The highest chance of success was observed after induction of labor where there are prior vaginal delivery and favorable cervix [90] Timothy *et al*. in their systematic review found few reserearcher reporting about slower labors even after using higher doses of vaginal misoprostol [91] while other reported that high doses of oral or vaginal misoprostol are quite effective at achieving vaginal delivery. Pevzner *et al*. revealed that duration of labor, oxytocin requirements, and cesarean delivery rates are significantly higher with increasing BMI in prostaglandin-induced women (Table 3) [72].

The studies by meta-analysis, RCT and many other methods found different rate of risk of cesarean section at the end of the induction of labor. The risk of cesarean section depends on maternal factors such as age, parity, BMI, cervical score, baby size, medical, and obstetrical conditions complicating pregnancy. However, most of the studies found the induction is associated with more cervical ripening and successful vaginal delivery [6,14,69-70,76,98]. While few studies found the induction results in higher rate of cesarean delivery compared to expectant management [22,19,104].

Summary

This study tried to highlight various indications for which an induction of labor is decided for a woman. The common indications were post-term pregnancy, term PROM, hypertensive disorders, intrauterine fetal distress, fetal death, gestational diabetes, and other fetal indications. Among these, the most common indication was postdated pregnancy. The failure of induction with cesarean section was varied from 3% to 48.7%. However, most of the studies found higher rate of successful delivery after induction. The reason for which cesarean section was

Table 3: The net outcome after induction of labor

Author	Year	Research design	Net outcome (rate of cesarean section)
Mishanina *et al*. [48]	2014	Systematic review and meta-analysis	Decreased
Hofmeyr and Gulmezoglu [92]	2001	Systematic review	Decreased
Wood *et al*. [93]	2014	Meta-analysis	Decreased
Gulmezoglu *et al*. [47]	2006	Systematic review	Decreased
Gulmezoglu *et al.* [94]	2012	Systematic review	Decreased
Sanchez Ramos *et al*. [29]	2003	Systematic review	Decreased
Alfirevic *et al*. [76]	2014	Systematic review	Decreased
Alfirevic *et al*. [95]	2000	Systematic review	Decreased
Boulvain *et al*. [30]	2008	Systematic review	Decreased
Vogel *et al.* [35]	2013	Systematic review	Decreased
Crowley [96]	2000	Systematic review	No difference
Boulvain *et al.* [73]	2016	Systematic review	Not clear
Guerra *et al.* [26]	2009	Secondary analysis	Decreased
Cheng [97]	2008	RCT	Decreased
Koopmans *et al.* [98]	2009	RCT	Decreased
Pennel *et al.* [99]	2009	RCT	Increased
Bhutto *et al.* [100]	2013	RCT	Nil
Hermus *et al*. [101]	2009	Cohort	No difference
Marry *et al*. [37]	2015	Cohort	Decreased
Yeast *et al.* [102]	1999	Cohort	Decreased
Nooh *et al*. [103]	2005	Retrospective	Decreased
Dubline *et al.* [19]	2000	Cohort	Increased
Johnson *et al.* [104]	2003	Cohort	Increased
Verhoeven *et al.* [22]	2012	Case control	Increased

done were failed induction, fetal distress, meconium stained liquor, undiagnosed CPD, and nonprogress of labor. The factors independently predicted the risk of cesarean section were age of mother, parity, BMI, cervical factors, indications, doses of drug and weight of baby. Most of the systematic reviews showed decreased rate of c-section after induction in term pregnancy. Hence, it is clear from the findings that induction of labor is beneficial in reducing the risk of cesarean section with better perinatal outcomes.

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