Definition of Failed Induction of Labor and Its Predictive Factors: Two Unsolved Issues of an Everyday Clinical Situation

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Key Words
Induction of labor · Failed induction of labor · Predictive factors · Transvaginal ultrasound

Abstract
Objective: The objectives of this review were to identify the predictive factors of induction of labor (IOL) failure or success as well as to highlight the current heterogeneity regarding the definition and diagnosis of failed IOL. Materials and Methods: Only studies in which the main or secondary outcome was failed IOL, defined as not entering the active phase of labor after 24 h of prostaglandin administration ± 12 h of oxytocin infusion, were included in the review. The data collected were: study design, definition of failed IOL, induction method, IOL indications, failed IOL rate, cesarean section because of failed IOL and predictors of failed IOL. Results: The database search detected 507 publications. The main reason for exclusion was that the primary or secondary outcomes were not the predetermined definition of failed IOL (not achieving active phase of labor). Finally, 7 studies were eligible. The main predictive factors identified in the review were cervical status, evaluated by the Bishop score or cervical length. Discussion: Failed IOL should be defined as the inability to achieve the active phase of labor, considering that the definition of IOL is to enter the active phase of labor. A universal definition of failed IOL is an essential requisite to analyze and obtain solid results and conclusions on this issue. An important finding of this review is that only 7 of all the studies reviewed assessed achieving the active phase of labor as a primary or secondary IOL outcome. Another conclusion is that cervical status remains the most important predictor of IOL outcome, although the value of the parameters explored up to now is limited. To find or develop predictive tools to identify those women exposed to IOL who may not reach the active phase of labor is crucial to minimize the risks and costs associated with IOL failure while opening a great opportunity for investigation. Therefore, other predictive tools should be studied in order to improve IOL outcome in terms of health and economic burden.

Introduction

The induction of labor (IOL) has become more frequent in recent years, occurring in about 20% of almost all settings [1, 2]. Concerns about IOL indications, management and outcomes are rising in proportion to this rate. The IOL is defined as the artificial initiation of labor.
[3]. On the other hand, cervical ripening is defined as a prelude to the onset of labor, whereby the cervix becomes soft and compliant, either occurring naturally or as a result of physical or pharmacological interventions [3]. Cervical ripening by physical or pharmacological methods and labor induction should not be confused, even though the literature usually refers to labor induction as the process also including cervical ripening. Although the definition of labor induction is simple, criteria for successful and failed IOL have not been standardized and no consensus has been reached to date. Regarding IOL outcome, a variety of endpoints such as mode of delivery (vaginal delivery or cesarean section), vaginal delivery within a certain time interval or achievement of the active phase of labor have been suggested. As a consequence, comparison between published studies becomes a complicated issue due to the existing heterogeneity in the literature.

**Definition of IOL, Failed IOL and Cesarean Section for Failed IOL**

Some authors have expressed their concerns about IOL and the definition of failed IOL [1, 2]. Lin and Rouse [2] suggested a practical definition of failed IOL, which should maximize the number of women progressing to the active phase of labor while maintaining a low incidence of adverse maternal and neonatal outcomes. They define failed IOL as the inability to achieve cervical dilatation >4 cm after 12 ± 3 h of oxytocin administration (with a goal of 200–225 MVU or 3 contractions/10 min). As Caughey et al. [4] mentioned in their article, since the purpose of IOL is to cause a nonlaboring woman to go into labor, a reasonable definition would be to achieve active labor as a measure of success. Consequently, this was the main outcome assessed in our review. Nonetheless, most authors propose vaginal delivery as the main IOL outcome, although it depends on many other factors interacting during labor which are not necessarily related to the induction process.

Another important aspect to consider is that failed IOL diagnosis at a given time point does not always involve the performance of an immediate cesarean section in all centers. This can be explained by several studies which have shown that, continuing the induction process beyond a failed IOL diagnoses at a given time point will lead to vaginal delivery in a considerable number of cases. Women who progressed into active labor within 12 h had a 67–86% probability of achieving vaginal birth, whereas only 31–33% of women who reached active labor after 18 h had a vaginal delivery [5]. Consequently, failed IOL diagnosis does not always involve performing a cesarean section for failed IOL and, therefore, the reported rates of these two events vary between studies. In addition, the majority of guidelines do not specify a time limitation from the initiation of IOL to delivery [3], and neither has consensus about the duration of the latent and active phase been reached. The latent phase is defined as the period of time, not necessarily continuous, when there are painful contractions and some cervical change including cervical effacement and dilatation up to 4 cm, and the onset of active labor when there are regular painful contractions and there is progressive cervical dilatation from 4 cm [6].

Despite the lack of specific recommendations, a definition of failed IOL which coincides in time with a low probability to achieve the active phase of labor seems to be the best option. Adverse outcomes related to the length of latent phase have not been extensively evaluated, although some studies have related a prolonged latent phase with subsequent labor abnormalities and the need for cesarean section [7]. A prolonged latent phase of over 12 h was also associated with a significantly longer duration of active labor [8]. Nevertheless, higher rates of chorioamnionitis (from 20–22 to 25–27%) and postpartum hemorrhage (from 11 to 16%) have been reported after 6 and 12 h of latent phase, respectively [5, 9]. In addition, economic costs related to the duration of IOL must also be taken into account [10]. This is important information which, combined with other prognostic factors, could help in the decision as to whether continuing the induction process is worthwhile or not.

In summary, it is essential to diagnose failed IOL at an appropriate time in order to counsel the patients and to decide whether to continue with the IOL or to perform a cesarean section based on the low probability of entering the active phase of labor without increasing the adverse outcomes [11]. The main objectives of this review were to identify the predictive factors of IOL failure or success as well as to highlight the current heterogeneity regarding the definition and diagnosis of failed IOL that could impair the identification of prognostic factors.

**Material and Methods**

**Identification of the Literature**

An electronic database search (PubMed, MEDLINE and Embase) up to January 2014 was performed. The search strategy for identification of studies on outcome of IOL and its predictive factors consisted of the following MeSH term combination: ‘induced, labor’, ‘treatment outcome’, ‘ultrasonography’ and ‘cervix uteri’.
We checked the reference lists of relevant studies to identify cited articles not captured by the electronic searches, and the ‘related articles’ function in PubMed was used to complete the search. Two investigators (N.B., F.M.) independently screened titles and abstracts of electronic search results for relevance. Full texts of potentially eligible citations were obtained for further assessment. Screening for inclusion and data extraction were carried out by one reviewer (N.B.) and was checked by a second reviewer (F.M.). We included retrospective and prospective studies, as well as systematic reviews and meta-analyses. Restrictions regarding the indication of IOL or the method of induction were not applied. The studies were included only if their main or secondary outcome was failed IOL defined as not entering the active phase of labor after 24 h of prostaglandin administration ± 12 h of oxytocin infusion. The data collected were: study design, exact definition of failed IOL, induction method, IOL indication, failed IOL rate, cesarean section because of failed IOL and predictors of failed IOL.

Results

Description of the Studies

The database search detected 507 publications. After the first review of the titles and abstracts, 427 were excluded. The full texts of 80 articles were obtained. The main reason for exclusion was that the primary or secondary outcomes were not the established definition of failed IOL (not achieving active phase of labor) as shown in figure 1. Finally, 7 studies were eligible. In 5 of the 7 studies included, achieving the active phase of labor was the main outcome assessed. In two studies, not entering the active phase of labor was the secondary outcome [12, 13], and these were also included in the review. The characteristics of the studies included are summarized in table 1.

Indication for IOL

Medical and elective IOL should be differentiated since IOL outcomes vary in relation to induction indication. When there is a medical indication, the potential benefit for the mother or the fetus easily supersedes the IOL risks. Recommendations for IOL for postterm gestation, preterm rupture of membranes at term and premature rupture of membranes near term with pulmonary maturity are supported by the evidence. In these IOL sit-
uations, an increased rate of caesarean section is not observed [14]. Intrauterine growth-restricted fetuses show higher intra-uterus mortality in the expectant group balanced by an increase in neonatal deaths in the immediate induction group. There is little evidence regarding insulin-requiring diabetes, twin gestation, fetal macrosomia, oligohydramnios, cholestasis of pregnancy, maternal cardiac disease and fetal gastroschisis [1, 14]. Postterm pregnancy is by far the most frequent IOL indication. On the other hand, elective IOL is becoming a more frequent IOL indication especially based on the latest scientific evidence [15]. Despite the low risk of maternal and fetal complications related to elective IOL, favorable cervical and obstetrical conditions should be a prerequisite when indicating elective IOL in order to further decrease the potential adverse outcomes associated with this intervention. IOL indications are shown in table 2. In the studies included in our review, the elective induction rate varies from 0.95 to 10%, showing a progressive increase in almost all settings. In one study [12] IOL indications were not reported.

Rates of Cesarean Section for Failed IOL
A higher rate of maternal and fetal morbidity especially with an increased risk of cesarean section has been associated with IOL [16, 17], but this association has been challenged in recent years. A Cochrane review concluded that cesarean section rates and assisted vaginal delivery rates are not increased by IOL at term when a medical indication exists [18, 19]. It has been demonstrated that the cesarean rate does not increase, or it even decreases with a policy of IOL at or beyond 41 weeks of gestation.

### Table 2. Indications for IOL

<table>
<thead>
<tr>
<th>First author</th>
<th>n</th>
<th>Postterm</th>
<th>Hypertensive diseases</th>
<th>Diabetes</th>
<th>IUGR</th>
<th>Fetal macrosomia</th>
<th>Oligohydramnios</th>
<th>Elective</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenakis [36]</td>
<td>597</td>
<td>22%</td>
<td>32%</td>
<td>16%</td>
<td>18%</td>
<td>7 (6.60)</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roman [37]</td>
<td>106</td>
<td>61 (51.55)</td>
<td>2 (1.89)</td>
<td>4 (3.77)</td>
<td>4 (3.77)</td>
<td>28 (26.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang [23]</td>
<td>105</td>
<td>41 (39.05)</td>
<td>5 (4.76)</td>
<td>2 (1.90)</td>
<td>3 (2.86)</td>
<td>27 (25.71)</td>
<td>1 (0.95)</td>
<td>1 (0.95)</td>
<td></td>
</tr>
<tr>
<td>Park [24]</td>
<td>161</td>
<td>41 (25.47)</td>
<td>2 (1.24)</td>
<td>7 (4.35)</td>
<td>19 (11.80)</td>
<td>9 (5.59)</td>
<td>6 (3.73)</td>
<td>10 (6.21)</td>
<td></td>
</tr>
<tr>
<td>Park [25]</td>
<td>110</td>
<td>30 (27.27)</td>
<td>6 (5.45)</td>
<td>5 (4.55)</td>
<td>6 (5.45)</td>
<td>11 (10)</td>
<td>34 (30.91)</td>
<td>11 (10)</td>
<td>18 (16.36)</td>
</tr>
<tr>
<td>Frederiks [13]</td>
<td>400</td>
<td>165</td>
<td>111</td>
<td>45</td>
<td>83 (20.75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses indicate percentages. Premature rupture of membranes was not reported in any of the studies. IUGR = Intrauterine growth restriction.
in addition to improving perinatal outcomes [15, 20]. Conflicting results are reported below 40–41 weeks of gestation [21, 22].

All the data cited suggest that in the next years the number of IOL may increase further. Consequently, it is of paramount importance to reach consensus on the management of this extremely frequent intervention.

As mentioned above, the diagnosis of failed IOL does not always imply performing a cesarean section at this time. In addition, not all the studies included in the review reported both failed IOL diagnosis and cesarean section for failed IOL rates as shown in table 3. Nevertheless, despite the limited number of studies, a nonnegligible proportion of patients underwent a vaginal delivery after being diagnosed with failed IOL in 3 of the 7 studies included [23–25].

Factors Determining IOL Outcome

Despite the large number of studies conducted, no good predictive factors were found to successfully identify the group of patients who will not respond to physical or pharmacological induction, and hence achieve the active phase of labor. Heterogeneity between the outcomes assessed contributes to the lack of conclusive results.

Cervical status, mainly measured by the Bishop score and parity, has been shown to be the main predictor of successful labor induction [26, 27]. Other predictors such as maternal age, weight, height, body mass index, ethnicity and socioeconomic status have been reported. Obstetric and medical history such as gestational age at delivery, birth weight and amniotic fluid index have also been described [28]. The relevant predictive factors reported in the studies included in the review are shown in table 4.

Gestational Age

Placental function declines while fetal intolerance to labor and fetal weight increases with gestational age. All these factors could contribute to increasing the rate of cesarean section. However, not entering the active phase of labor, and therefore failed induction, are not related to the three factors described above [29]. Earlier gestational age was found to be a significant predictive factor for failed IOL in one of the studies included [24].

Maternal Characteristics

Maternal age contributes to a higher prevalence of maternal complications during pregnancy and therefore to an increased rate of IOL, including those with unfavor-
Cervical Status

As prelabor cervical status has been recognized as the most important predictor of induction success, many studies have evaluated the relationship between the Bishop score and sonographic cervical characteristics with IOL outcome. Regarding the predictive value of the Bishop score, a meta-analysis [34] and a recently published systematic review [35] reached divergent results. Teixeira et al. [34] concluded that the Bishop score still seems to be the most accurate predictive factor of vaginal delivery after IOL. When referring to achieving the active phase of labor, either with no time limit for this to occur or within a certain time interval, the same conclusion cannot be assumed due to lack of studies assessing this outcome. On the other hand, Kolkman et al. [35] showed that a Bishop score of 4, 5 or 6 was a poor predictor of IOL success if that was defined as achieving a vaginal delivery. For the prediction of cesarean delivery, the sensitivity and specificity of a Bishop score <6 was 78 and 44%, respectively, and of a Bishop score <9 was 95 and 30%. This study recommended not using the Bishop score in decision making. Three of the studies included in our review [25, 36, 37] found the Bishop score to be a significant predictive factor of IOL outcome, although it was not a strong predictor in any of the studies. Cervical dilatation and cervical effacement were independently associated with ‘achieving active phase of labor’ in one study [12]. The Bishop score was not an independent predictive factor in the other studies included (table 4).

Regarding sonographic cervical assessment to predict IOL outcome, conflicting results are also reported. A recent meta-analysis found limited value of cervical length and cervical wedging in predicting the outcome of labor in clinical practice [38]. Moreover, of the 31 studies included in the meta-analysis only 2 reported the outcome ‘not achieving the active phase of labor’. The sensitivity and specificity of cervical length in the studies included in that review were 56–66% [37] and 83–75% [23], respectively, for a cutoff of 30 mm. In another systematic review, Hatfield et al. [26] also concluded that sonographic cervical length was not an effective or, at most, a weak predictor for any of the outcomes assessed (mode of delivery, vaginal delivery within 24 h and achievement of the active phase of labor). Moreover, when comparing the Bishop score with cervical length measured by ultrasound, sonographic cervical length was not superior to the Bishop score. Cervical length was found to be an independent predictive factor in 2 of the studies included in our review [23, 24]. Other sonographic characteristics studied such as cervical wedging (sensitivity 37%, specificity 80%) [38] and fetal head position (sensitivity 39%, specificity 71%) have not been shown to be good predictors [39].

To summarize, there is an association between the Bishop score and cervical length measured by ultrasound and IOL outcome, but this relation does not always result in a good predictor. Therefore, future studies should explore other cervical characteristics, a combination of factors or focus on new diagnostic tools.

Some predictive models have been developed to predict cesarean section risk after IOL [40–42], although none of these models evaluated the prediction of achieving the active phase of labor. Moreover, their use in clinical practice is not recommended due to their moderate predictive capacity [43].

Other Prognostic Factors
Biochemical Markers

Biochemical markers, such as fetal fibronectin and IGFBP-1, have also been studied, but neither have shown to be superior to the Bishop score regarding the prediction of successful IOL [44–46].

New Predictive Factors Based on Image Analysis

A wide range of technologies and devices assessing cervical characteristics are under development, but only two have been evaluated in women undergoing IOL: light-induced fluorescence (LIF) and elastography.

A method to measure cervical collagen using LIF has been developed [47, 48]. Fittkow et al. [49] found that LIF measurements correlate negatively with gestational age and positively with the time to delivery, although the correlation was weak. They applied this technique to assess cervical ripening in an IOL setting. LIF and the Bishop score were measured at the beginning of IOL. No correlation was found between the two parameters. The same measurements were performed 4 h after prostaglandin administration, finding a statistically significant inverse correlation. On the other hand, elastography is based on determining motion in areas of the cervix relative to others, defining an elastography index (EI). In a study of 29 women undergoing IOL, those with successful IOL had a higher EI of the internal os than those with failed IOL. The EI was not predictive in other cervical regions. Muscatello et al. [50] also reported higher rates of cesarean section in those women with a higher EI. However, a re-
cent study showed that elastographic score at the internal os was unlikely to be useful in the prediction of vaginal delivery and induction-to-delivery interval [51]. A technical limitation is that this measurement still depends on the force exerted by the operator and, therefore, further investigation is needed [52].

A variety of other techniques and devices are being investigated to determine cervical composition and behavior, although up to now they are only focused on preterm birth prediction [53]. Some examples of these methods are acoustic attenuation [54] and electric impedance [55] which assess cervical hydration. Second harmonic generation [56], Raman spectroscopy [57, 58] and backscattered power loss [58] also study cervical collagen microstructure. Regarding the assessment of tissue elasticity, several strategies such as the cervical consistency index [59] and a cervical aspiration device [60] have also been evaluated. The absence of the cervical gland area has also been proposed as a predictor of preterm birth [61, 62].

To summarize, there are a large number of studies describing new parameters to better assess cervical changes during pregnancy, thereby reflecting the strong interest of the scientific community in finding an objective and applicable evaluation method to predict relevant clinical outcomes such as IOL failure or success and preterm birth risk. Unfortunately, despite being very common situations, a robust predictor has not as yet been found.

Discussion

IOL is an extremely common procedure performed in all obstetrical settings. In about 20% of pregnancies, labor is induced for a variety of reasons, postterm pregnancy being the most frequent indication. Despite its enormous medical and economic impact, there are still many controversies regarding IOL definition, indications, management and outcomes. Heterogeneity between IOL protocols and definitions makes it very difficult to draw conclusions based on published studies.

The first aspect to highlight is the lack of a generally accepted definition of failed IOL. Most studies define failed IOL as the impossibility to achieve a vaginal delivery, although there are many other factors appearing during labor that may hinder or prevent a vaginal delivery, which may explain why a robust predictor has not been found. From our point of view, the definition of failed IOL should be consistent with the IOL definition itself, which is the achievement of the active phase of labor. Therefore, failed IOL should be defined as the inability to achieve this. An important finding of this review is that only 7 of all the studies reviewed assessed achieving the active phase of labor as a primary or secondary IOL outcome. This implies that most of the existing literature is based on a very general outcome, evaluating a final result such as the vaginal delivery, and therefore, adding confounding factors.

The second important conclusion of this review is that clinical risk factors themselves have a too low predictive value to be translated into a useful clinical tool. In contrast, cervical status remains the most important predictor of IOL outcome, although the value of the parameters explored to date is limited. Consequently, great efforts are being made in order to find an objective method to better assess cervical status. To find or develop predictive tools to identify those women exposed to IOL who may not reach the active phase of labor is crucial to minimize the risks and costs associated with IOL failure.

To conclude, a generally accepted and adequate definition of failed IOL is an essential requisite to analyze and obtain solid results and conclusions. On the other hand, improving the prediction of IOL failure is currently a major challenge in obstetrics due to the negative impact of a failed IOL in several fields. Our inability to predict this leads to long and expensive labor inductions. The identification of such women would allow individualized counseling and potentially improve outcomes in terms of health (adverse perinatal and maternal outcomes due to prolonged labor inductions), economic burden (costs in terms of staff, medication and hospitalization) and health system quality perception (maternal discomfort). Therefore, new predictors for this frequent intervention are urgently needed in order to improve IOL management and outcome.

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In the article by Baños N, Migliorelli F, Posadas E, Ferreri J and Palacio M, entitled 'Definition of failed induction of labor and its predictive factors: two unsolved issues of an everyday clinical situation' [Fetal Diagnosis and Therapy 2015;38:161–169, DOI: 10.1159/000433429], the following changes in the author affiliations need to be added:

Núria Baños\textsuperscript{a} Federico Migliorelli\textsuperscript{a} Eduardo Posadas\textsuperscript{a} Janisse Ferreri\textsuperscript{a} Montse Palacio\textsuperscript{a, b}

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Furthermore, we would like to give a new email address (NBANOS@clinic.cat) and we would like to add the following acknowledgments:

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