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Induction of labor in obese women

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ABSTRACT

People with obesity may require induction of labour (IoL) due to a higher incidence of pre-existing comorbidities and pregnancy complications, as well as to prevent post-term pregnancies and late-term stillbirths. IoL at 39 e 40 weeks is associated with fewer caesarean births and lower morbidity for the pregnant person and neonate when compared with expectant management. Ensuring the success and safety of IoL in people with obesity requires adherence to evidence-based protocols for the management of labour induction and augmentation. Cervical ripening as well as the latent and active phases of labour in people with obesity may be considerably prolonged, requiring higher cumulative doses of oxytocin. This should be guided by intrauterine pressure catheters and early provision of neuraxial analgesia, where possible. There is insufficient evidence to recommend one method of IoL over another. The need for higher doses of prostaglandins and concurrent agents for cervical ripening should be studied in prospective studies.

Introduction

Obesity is recognized as a prevalent chronic disease, complex, progressive, and recurrent, characterized by the presence of abnormal or excessive body fat (adiposity) that harms health [1]. According to recent data (2017-2018) from the United States, the prevalence of obesity among women aged 20-39 was 39.7%, varying significantly among racial/ethnic groups (17.2% among non-Hispanic Asians vs 56.9% among non-Hispanic Blacks) [2]. Obesity is not only a concern for people in high-income countries like the United States. An analysis of 1698 population-based measurement studies with 19.2 million participants in 200 countries has shown that by 2025, the global prevalence of obesity in women is expected to be >21% [3]. The management of pregnant individuals with obesity is therefore a global concern. Obesity is operationally defined as a body mass index (BMI) greater than 30 kg/m2 and is further categorized into class 1 (30-34.9 kg/m2), class 2 (35-39.9 kg/m2), and class 3 (40 kg/m2) [4]. Although this classification system is useful for population

Increased Preexisting and Pregnancy-Related Conditions Warranting Labor Induction

A recent systematic review of population-based studies, including 3.7 million pregnancies, showed that compared to individuals with a BMI of 18.5-24.9 kg/m2, those with a BMI of 40 kg/m2 had a significantly higher prevalence of preexisting diabetes (0.7% vs 4.1%) and essential hypertension (0.7% vs 8.9%) [26]. Additionally, these individuals were at significantly higher risk of developing gestational diabetes (3.9% vs 17%), pregnancy-related hypertensive disorders (3.5% vs 15.9%), and fetal macrosomia (6.2% vs 12.9%) [Fig. 2] [14]. Fetal macrosomia can also occur in the absence of diabetes due to increased placental secretion of adipokines (such as leptin and insulin [27]), which are important mediators of fetal growth. Pregnancy-related hypertensive disorders [28], diabetes [29], and macrosomia [29] are common indications for an increased rate of labor induction in individuals with obesity. Women with obesity are also at higher risk of fetal growth restriction [30-32], another significant indication for labor induction in contemporary clinical practice.

Reducing the Risk of Term Stillbirth

A U.S.-based population cohort study involving 2.8 million singleton fetal births demonstrated an association between obesity and stillbirth, with a hazard ratio of 2.48 for those with a BMI >40 kg/m2 and 3.16 with a BMI >50 kg/m2 [33]. Furthermore, maternal obesity was associated with 25% of all stillbirths occurring between 37 and 42 weeks of gestation, with the highest risk observed after 39 weeks of gestation [33]. Avoiding late-term stillbirth has, therefore, become another significant reason for labor induction in pregnancies complicated by obesity.

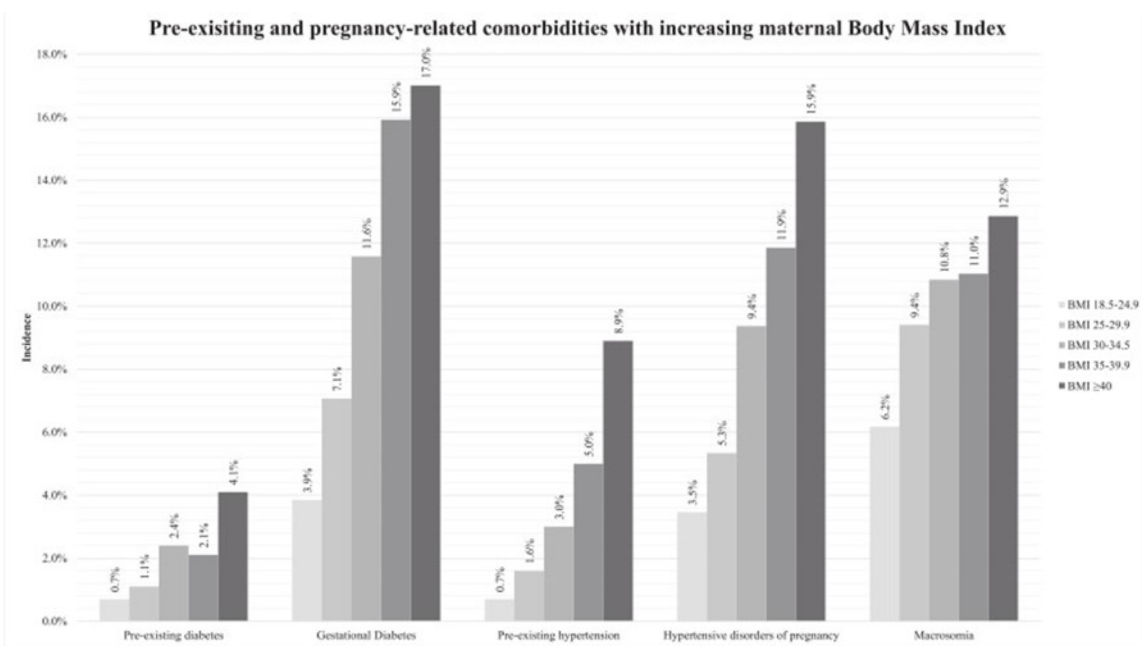

Fig. 2. Preexisting and Pregnancy-Related Comorbidities with Increasing Maternal Body Mass Index

studies, it has limited applicability to individuals in clinical practice. Clinical practice guidelines [5] increasingly use alternative classifications such as the Edmonton Obesity Staging System (EOSS) [6], which considers metabolic, physical, and psychological parameters (Fig. 1). The EOSS, focusing on the presence or extent of comorbidities and functional limitations, is more suitable for guiding clinical decision-making and predicting adverse clinical events than BMI or waist circumference measurements alone [7,8].

Indications for Labor Induction in Women with Obesity

A population-based cohort study involving 279,521 singleton pregnancies in the state of Ohio, United States, demonstrated that the rates of labor induction increased from 28% in those with a BMI of 18.5-24.9 kg/m2 to 34% in those with a BMI of 40 kg/m2 [9]. The rise in the rate of labor induction in this population, as confirmed by numerous other studies [10-14], can be attributed to several reasons.

Post-term Pregnancies

There is strong evidence that continuing pregnancies beyond 41-42 weeks of gestation, even in the absence of maternal and fetal risk factors, is associated with an increased risk of perinatal mortality and morbidity [15]. Labor induction between 41 and 42 weeks of gestation to prevent these complications is therefore encouraged by most clinical guidelines [16-18]. There is a positive correlation between obesity and post-term pregnancy [19, 22]. This can be explained by alterations in the activity of the hypothalamic-pituitary-adrenal axis in pregnant women with obesity [23]. Lower levels of circulating cortisol and corticotropin-releasing hormone have been observed in pregnant women with obesity compared to those without obesity [24]. An altered estrogen-progesterone ratio due to excess adipose tissue in women with obesity could be another possible explanation [25].

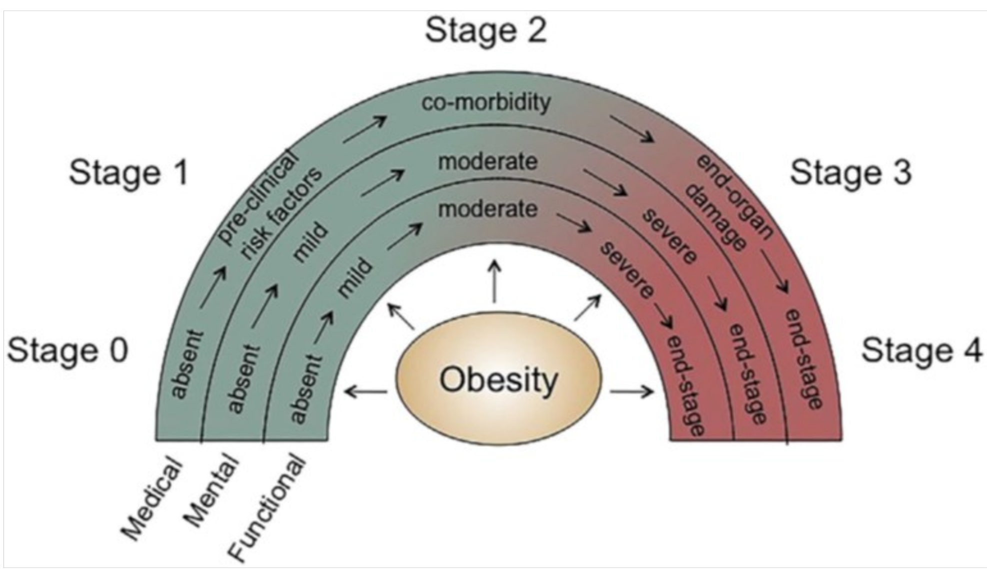

Fig. 1. Edmonton Obesity Staging System (EOSS), a system for stratifying the presence and severity of weight-related health issues in clinical and community settings.

Safety and Optimal Timing of Labor Induction in Women with Obesity

Labor Induction vs Expectant Management

Due to the higher incidence of comorbidities, pregnancy complications, the risk of stillbirth, and post-term pregnancies, it's not surprising that elective term labor induction is associated with lower maternal and neonatal morbidity in this population compared to expectant management [34,35]. A retrospective cohort study involving 165,975 births in California at or after 39 weeks of gestation in women with a BMI >30 kg/m2 showed that compared to expectant management, labor induction at 39 weeks of gestation in nulliparous women is associated with a lower rate of cesarean sections (35.9% vs 41%, adjusted odds ratio (aOR) 0.82, 95% CI 0.77-0.88), a lower incidence of severe maternal morbidity (5.6% vs 7.6%, aOR 0.75, 95% CI 0.65-0.87), and a lower number of admissions to neonatal intensive care units (NICUs) (7.9% vs 10.1%, aOR 0.79, 95% CI 0.70-0.89) [34]. Similar patterns were observed among multiparous women induced vs those managed expectantly at 39 weeks [cesarean sections 7.0% vs 8.7%, aOR 0.79 (95% CI 0.73-0.86), severe maternal morbidity 3.3% vs 4.0% aOR 0.83 (95% CI 0.74-0.94), and NICU admission 5.3% vs 7.4, aOR 0.75 (95% CI 0.68-0.82)], and for all women undergoing induction at 40 weeks regarding cesarean section [34]. A previous study involving women with a BMI of 30 kg/m2 in the absence of medical comorbidities demonstrated benefits in reducing cesarean sections with labor induction at 39 weeks in both nulliparous and multiparous women, but this benefit was not seen with inductions at 40 or 41 weeks of pregnancy [36]. A propensity score-matched study using data from the U.S. Centers for Disease Control and Prevention, involving 197,343 individuals with BMI 30.0 kg/m2 and singleton pregnancies induced at 39 weeks and 986,715 women managed expectantly, showed a lower risk of cesarean section with induction at 39 weeks (aOR 0.59, 95% CI 0.58-0.60), greater in multiparous women (aOR 0.47, 95% CI 0.46-0.49), and was reproducible across all obesity categories [37]. While some studies have been unable to demonstrate a reduction in cesarean sections through induction at 39 weeks, there is confirmation that labor induction at 39 weeks does not increase the risk of cesarean section [35,38].

Labor Induction vs Planned Cesarean Section

Individuals with a BMI >40 kg/m2 and a prior cesarean section appear to benefit from a repeat cesarean section compared to a trial of labor after cesarean (TOLAC) as it is associated with a lower incidence of uterine dehiscence (RR 2.20, 95% CI 1.0, 4.8), endometritis (RR 2.22, 95% CI 1.6, 3.1), low 5-minute Apgar scores (RR 2.95, 95% CI 2.0, 4.3), and neonatal birth trauma (RR 4.6, 95% CI 1.77, 12.03) [39]. Even in terms of cost, a repeat cesarean section has been considered cost-effective for individuals with a BMI >40 kg/m2 and a prior cesarean section [40]. However, the optimal mode of delivery for individuals with a BMI >40 kg/m2 and no prior cesarean section remains to be defined.

A recent Canadian study compared adverse neonatal outcomes, including death, neonatal intensive care unit admission, 5-minute Apgar score <7, or umbilical artery pH <7.1, in 8752 patients with a BMI >35 kg/m2, based on the mode of delivery [41]. This study showed that while adverse neonatal outcomes were lower with a successful vaginal delivery compared to a planned cesarean section (aOR 0.67, 95% CI 0.50-0.91), they were considerably higher with an unplanned intrapartum cesarean section (aOR 1.74, 95% CI 1.21, 2.48) [41]. A systematic review examining birth outcomes in individuals with a BMI >40 kg/m2 that differentiated between planned and actual modes of delivery showed that a successful vaginal delivery had a lower risk of postpartum hemorrhage (relative risk (RR) 0.21, 95% CI 0.19-0.23) but a higher risk of neonatal birth trauma (RR 6.56, 95% CI 1.26-34.10) compared to an intrapartum cesarean section. However, in the case of an attempted vaginal delivery (whether vaginal or intrapartum cesarean section), there was a higher risk of postpartum hemorrhage (RR 2.67, 95% CI 1.52, 4.69) but a lower risk of wound complications (RR 0.54, 95% CI 0.33, 0.87) compared to those undergoing a planned cesarean section [39]. These studies indicate that individuals with a BMI >40 kg/m2 may have a successful vaginal delivery associated with better maternal outcomes compared to a planned cesarean section; however, the possibility of an intrapartum cesarean section may carry a higher risk of maternal complications. Since the success of vaginal delivery cannot be guaranteed at the time of labor induction, the likelihood of needing an emergency cesarean section appears considerably higher with a BMI >40 kg/m2 [26], and cesarean sections in these individuals may pose risks to the anesthesia and surgical teams, leading to significant maternal and neonatal morbidity [42]. The option of a planned cesarean section performed by an experienced surgical team remains a viable option, at least in clinical settings with ample resources.

A cost-minimization analysis comparing labor induction with planned cesarean section showed that labor induction was the preferred cost-effective strategy in terms of both direct and total costs as long as the probability of vaginal delivery after induction was >57% [40]. A more recent cost-effectiveness analysis also demonstrated that labor induction in individuals with a BMI >40 kg/m2 is cost-effective compared to a planned cesarean section, unless the cesarean section rate following induction exceeds 70% [43]. Currently, there appears to be a clinical equipoise regarding the optimal mode of delivery in women with a BMI >40 kg/m2 and no prior cesarean section. Until a randomized study can determine the safest mode of delivery in this population, the scientific evidence supports the implementation of planned labor induction at 39-40 weeks of gestation in women with a BMI >40 kg/m2 and no previous cesarean delivery.

The Effectiveness of Labor Induction in Women with Obesity

While labor induction in women with obesity is associated with clinical benefits and a lower rate of cesarean sections compared to expectant management, obesity remains independently associated with an increased risk of cervical ripening failure. A study in the U.S. population that included 1,098,981 individuals with a pre-pregnancy BMI >30 kg/m2 out of 19,844,580 live births found that the overall failure rate of labor induction was 24.9% with a BMI >30 kg/m2 compared to 17.2% in those with a normal BMI [44]. The increased risk of unplanned cesarean sections due to failed labor induction in individuals with obesity has been reported in several studies [9,10,12,42,45-48]. A recent meta-analysis of 10 cohort studies showed that women with obesity not only had a higher risk of requiring a cesarean section for failed labor induction compared to those with a normal BMI (OR 1.82, 95% CI 1.55, 2.12, p <0.001) but also required higher doses of prostaglandins for cervical ripening, higher doses of oxytocin for induction and augmentation of labor, and had a longer time to birth with or without the use of oxytocin [49]. Another systematic study, through the review and meta-analysis of population-based studies involving over 3.7 million births, highlighted that rate of unplanned cesarean sections increased in every BMI category from 13.9% in those with a normal BMI to 21.7% in those with a BMI >40 kg/m2 [26]. The increased risk of cervical ripening failure and the longer duration of latent and active phases of labor should be discussed before performing labor induction to ensure realistic expectations.

The optimal method for labor induction in women with obesity

There is a significant lack of high-quality data on the most effective methods for inducing labor in women with a BMI >30 kg/m2 [50]. A retrospective cohort study comparing labor induction with dinoprostone (n = 70) vs misoprostol (n = 72) vs cervical catheters (n = 50) among individuals with a BMI >25 kg/m2 showed no significant difference in the mean time intervals between labor induction and birth (dinoprostone 24.5 ± 15.2 vs misoprostol 28.7 ± 12.3 and catheters 25.1 ± 12.9 hours, p = 0.15) [51]. Other studies that demonstrated the benefit of one method over another did not include sufficiently large sample sizes or rules to eliminate all confounding factors that could influence the results. For example, a single-center retrospective cohort study of 709 patients showed that misoprostol, compared to mechanical methods for cervical ripening, was associated with a higher likelihood of requiring a cesarean section with cervical dilation <5 cm (24% vs 15%, p = 0.01) and any dilation (35% vs 26%, p = 0.03) [52]. It should be noted that the same dose of misoprostol was used in subjects with a BMI >30 kg/m2 as in those with a BMI <30 kg/m2 (25 mcg every hour for a maximum of six doses). Another single-center retrospective study comparing labor induction with oral or vaginal misoprostol (prostaglandin E1) vs dinoprostone (prostaglandin E2) in 564 individuals with a BMI >30 kg/m2 showed that the use of oral or vaginal misoprostol was associated with a higher likelihood of successful cervical ripening (78.1% vs 66.7%; aOR 1.58, 95% CI 1.06-2.36) and a lower risk of cesarean section (39.1% vs 51.3%; aOR 0.68, 95% CI 0.47-0.97) [53]. These results should be interpreted with caution due to the small number of women included and the possibility of suboptimal dosing. Until studies with a sufficiently large, investigated population using dosages of ripening agents that take into account the pharmacokinetics in women with obesity are published, the choice of labor induction method should consider prenatal outcomes, uterine activity, cervical status, and individual preferences [54].

Predictive Factors for Failed Labor Induction

Various prediction models have identified obesity as a significant predictive factor for the success of vaginal delivery after labor induction [55]. A recently published prediction model has shown that pre-pregnancy weight, BMI (which takes into account both height and weight), and BMI at birth (which considers gestational weight gain) were three of the seven independent predictive factors for a favorable vaginal delivery outcome after labor induction [56]. Among individuals with obesity, nulliparity, advanced maternal age, greater weight gain during pregnancy, higher BMI categories, and low Bishop scores at the time of labor induction have been demonstrated as independent predictive factors for the success of labor induction [22, 48, 57-60]. A predictive model specifically developed for individuals with obesity has recently been adopted, distinguishing those with an increased (>75%) vs decreased (<20%) risk of cesarean section [44]. This model, which includes maternal age, parity, height, birth weight, gestational weight gain, history of previous vaginal or cesarean delivery, history of preexisting diabetes and hypertension, and Medicaid insurance, has proven to be highly reliable [61].

Possible Reasons/Mechanisms Contributing to the Failure of Labor Induction in Individuals with Obesity

Several theories have been proposed to explain the higher risk of failed induction in individuals with obesity. A relative increase in distribution volume could have a dilutive effect on both the agent that causes cervical ripening (prostaglandins E1 and E2) as well as oxytocin during labor induction, potentially leading to reduced tissue response and the consequent need to increase drug doses and administration duration [9, 21, 45, 46, 48, 52, 62, 63].

A retrospective cohort study comparing the contraction rate in 313 individuals with a Bishop score <6 before and four times after the administration of misoprostol for labor induction demonstrated that, compared to those with a BMI <30 kg/m2, those with a BMI >30 kg/m2 had a lower mean number of contractions per hour (4 ± 5 vs 7 ± 5, $p < 0.001$) at all time points following misoprostol administration (first hour 5 ± 6 vs 9 ± 6, $p < 0.001$; second hour 9 ± 9 vs 15 ± 9, $p < 0.001$; third hour 13 ± 10 vs 17 ± 9, $p < 0.001$; fourth hour 14 ± 9 vs 20 ± 10, $p < 0.001$) [64]. This data could explain the prolongation of the latent phase of labor demonstrated in some studies [65].

Active labor, whether spontaneous or induced, is also more likely to last longer and progress abnormally in individuals with obesity [66-69]. In a multicenter retrospective study of 118,978 births stratified by BMI, those with a BMI >40 kg/m2 showed a higher median time to progress from cervical dilation of 4-10 cm (7.7 vs 5.4 hours for nulliparous women and 5.4 vs 4.6 hours for multiparous women) compared to those with a BMI <25 kg/m2 [69]. The study suggested that labor progresses more slowly as BMI increases, highlighting the need to adjust labor management to allow for longer labor times in consideration of these differences [69]. A secondary analysis of a multicenter, double-blind, randomized study showed an increased median time to birth in obese subjects (27 hours for BMI >40 kg/m2 vs 22.7 hours in those with a BMI <30 kg/m2), regardless of whether labor induction was performed using extended-release vaginal inserts containing dinoprostone (prostaglandin E2) 10 mg, misoprostol (prostaglandin E2) 50 mg, or misoprostol 100 mg [46]. Prolonged intervals between labor induction and birth in individuals with obesity have been demonstrated in many other studies, irrespective of the induction method used [45, 49, 59, 62, 70]. A single-center study examining labor induction in individuals with a Bishop score <5 and comparing outcomes in those with BMI >40 kg/m2 to those with BMI <30 kg/m2 found that not only does the interval between labor induction and birth significantly increase in women with higher BMI, but women with BMI >40 kg/m2 also require more doses of misoprostol (2.32 vs 1.59, $p = 0.003$) and a longer duration of oxytocin administration before delivery (10.39 hours vs 7.17 hours, $p = 0.023$) [70].

Compared to individuals with a BMI <28 kg/m2, those with a BMI >40 kg/m2 require a higher average rate of maximum oxytocin dosage (17.7 mU/min vs 13.1 mU/min, $p = 0.001$) [65]. The need for higher doses and duration of oxytocin has been demonstrated in several studies [46, 70, 71], but not in all [59]. Individuals with obesity require higher cumulative doses of oxytocin after labor induction compared to those with a BMI of 18.50-24.99 kg/m2 (adjusted $R^2 = 0.194$, $p < 0.001$) [72]. A multicenter retrospective study involving 4284 births showed that individuals with a BMI >40 kg/m2 required a longer duration of oxytocin (10.7 hours vs 8.2 hours, $p < 0.001$) and had a higher maximum rate of oxytocin (10 mU/min vs 8 mU/min, $p < 0.001$). It was also more likely for them to require oxytocin rates >20 mU/min to achieve vaginal delivery (5% vs 2%, $p < 0.001$) [73].

The altered response to oxytocin in individuals with obesity may be linked to alterations in oxytocin receptor expression or function [74], which, in turn, may be responsible for decreased myometrial contractility [75] and a reduced response to oxytocin during labor induction. Higher levels of leptin, a hormone produced by adipose tissue in individuals with a BMI >30 kg/m2, reduce the influx of calcium ions into uterine smooth muscle [76], and also play an antagonistic role to oxytocin, which acts to induce myometrial contractions by releasing intracellular calcium [77].

Improving the Success and Safety of Vaginal Delivery After Labor Induction in Women with Obesity

The incidence of primary cesarean section due to failed labor induction or labor progress can potentially be reduced by considering higher cumulative doses of oxytocin to optimize uterine activity [72, 73] and using rigorous protocols for labor management after induction [78]. Monitoring uterine activity through external tocography is more challenging in this population, and an intrauterine pressure catheter should be placed for internal tocography once the membranes have ruptured. Intrauterine pressure catheters allow for the objective measurement of contraction strength and frequency and enable titration of oxytocin dosage using standardized Montevideo units, thus ensuring the safe use of higher doses of oxytocin that may be required in individuals with obesity. This is particularly important if the quality of contractions cannot be adequately assessed, as ineffective contractions put these individuals at risk of cesarean section for failed induction. If higher doses of cervical ripening agents such as prostaglandins can be safely used, the population can be studied in sufficiently large prospective trials.

It is also recommended that individuals with obesity be informed about the benefits of early neuraxial analgesia during labor [79, 80], as placing the neuraxial block can be challenging, and ensuring a well-functioning neuraxial block may obviate the need for general anesthesia in case of an urgent cesarean section. Individuals with obesity are also at a higher risk of neuraxial analgesia failure since they may require manipulation of the epidural catheter, increased subsequent doses, and more frequent administrations [81].

Conclusion

Individuals with obesity constitute a group for whom labor induction may be recommended due to pre-gestational comorbidities and pregnancy-related complications, as well as to reduce the risk of post-term pregnancies and fetal mortality at term. However, labor induction in this population may carry a higher likelihood of intrapartum cesarean section, leading to increased maternal and neonatal morbidity. While there may be potential benefits in performing planned cesarean sections in individuals with a BMI >40 kg/m2, conducted by expert teams, to reduce the morbidity associated with unplanned cesarean sections, currently, there is no high-quality evidence to recommend this practice.

Based on published evidence, labor induction between the 39th and 40th week can offer clinical and cost advantages. Healthcare providers should strive to increase the success of inductions through personalized care that includes choosing the most appropriate induction method based on clinical assessment and patient values, allowing sufficient time for labor progression with higher doses of oxytocin, if necessary, to optimize uterine activity, considering early administration of effective neuraxial analgesia, and adhering to strict protocols for labor management.

Further research is needed to determine the optimal dose of prostaglandins for cervical ripening and to assess whether planned cesarean sections may be preferred over labor induction in individuals with a BMI >40 kg/m2.

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