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Is it possible to safely prevent late preterm and early term births?

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A R T I C L E I N F O

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A B S T R A C T

Late preterm and early term birth is associated with adverse short- and long-term consequences, particularly for neurodevelopment. A clear reduction in these births can be achieved by avoidance of non-medically indicated births prior to 39 weeks gestation, as shown following the introduction of prohibitive policies in the USA. However, clinicians and policy-makers must always consider the potential for unintended adverse consequences of such action, such as a potential for an increase in term stillbirth. Finding the balance between optimising long-term neurological outcomes and avoiding rare but devastating term stillbirths is one of the challenges of modern maternity care. In this article we review the current evidence for whether this balance can be found, where early births can be safely prevented, and what remains to be addressed to optimise this balance safely.

1. Introduction

The traditional definition of preterm birth is that occurring before 37 weeks gestation. Although this definition is important for epidemiological studies, it suggests a dichotomy that does not hold true in clinical outcomes which occur, rather, in a spectrum. There is a clear association between gestation length and outcomes for the child, which, notably for long-term outcomes such as neurodevelopment, extends beyond 37 weeks into term gestations. This provides impetus for interventions aimed at reducing the rate of births before 39 weeks.

A potential unintended negative consequence of deferring iatrogenic early term births is an increase in adverse outcomes such as stillbirth. It is true that a fetus cannot be stillborn at 40 weeks if it was electively delivered at 37 weeks, and the fear of a late pregnancy disaster may entice clinicians to act earlier in a pregnancy where the individual adverse effects of such action are comparatively small. At a population level, however, the prevention of one stillbirth may come at the expense of a significant population shift toward subtle but significant adverse neurodevelopment that may be of greater societal burden. Finding this balance is part of the art of modern maternity care.

In light of the evidence of the benefits of avoiding birth before full term, various jurisdictions have employed strategies to achieve this in the clinical setting. The impact of such policies upon the rate of adverse perinatal outcomes has been the subject of debate. While there is now clear evidence that we can reduce the rate of early term births, in this article we review the evidence for whether this can be safely achieved.

2. Adverse consequences of late preterm and early term birth

Fetal maturation is a continuum and variable across organ systems. Compared to other mammals, humans give birth to relatively neurologically immature neonates as an evolutionary trade-off between fetal brain size and the pelvic capacity of a bipedal mother. With offspring who are already immature, shortening of gestational length, even by a small amount, has the capacity to deliver an infant with limited capacity to make a smooth transition to extrauterine life. The impact of a complicated neonatal transition may be lifelong. Further, the endocrine events of birth and their effects on organ development can influence critical events in the organ maturation sequence and impair their long-term function even in the absence of apparent neonatal complications.

2.1. Short-term outcomes

Late preterm infants are at increased risk of severe neonatal complications of prematurity compared to term infants. Bonnevier et al. showed a six-fold increase in neonatal death in late preterm compared to term infants as well as increases in neurological, respiratory, and infectious complications by 2.4, 7.7, and 2.3 times, respectively [1]. Not all of this increase in adverse perinatal outcomes is related to the cause of the preterm birth rather than the prematurity itself [2]. Respiratory complications, especially, appear to relate more directly to prematurity regardless of the underlying cause and, importantly, those neonates suffering respiratory distress syndrome are at greater risk of long-term neurodevelopmental morbidity than are those without [3,4].

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The rate of adverse perinatal outcomes in early term infants is low. Adverse events, including respiratory distress, feeding difficulty, hypoglycaemia, jaundice, nursery admission and possibly neonatal death are more common at 37–38 weeks than at 39 weeks [5]. This may be particularly important in infants born by caesarean section, compared to those born vaginally [6,7]. Maternal outcomes – aside from satisfaction, which is highly individually variable – are not significantly adversely affected by early term induction compared with expectant management and may be improved [8].

2.2. Long-term outcomes

The long-term outcomes of late preterm and early term birth are now well recognised. Such adverse consequences are primarily neurological and neurodevelopmental [9]. These concerns were initially noted by MacKay et al., who found increased requirement for special education among children born at 37, 38, and 39 weeks of 36%, 19%, and 9% over those born at 40 weeks [10]. Subsequent studies demonstrated similar associations between early term birth and adverse neurological outcomes [11–16]. Most fetal brain growth occurs in late gestation, with 50% of cortical volume increase occurring between 34 and 40 weeks, and interruption of this process leads to reduced white matter volume in adults born preterm, who have measurable deficits in IQ, academic achievement, and behaviour disorders [17–19].

Other associations between early term birth and adverse health outcomes have been demonstrated. For example, men born at early term have higher blood pressure than those born at full term, which may confer a greater risk of cardiovascular morbidity and mortality [19]. Again, subtle individual-level differences in physiology may have profound population-level implications.

3. Effectiveness of prevention strategies

Preventing late preterm and early term birth is encompassed within the goal of broader preterm birth prevention strategies. As the majority of preterm births occur at late gestations, any intervention aimed at reducing the overall rate is likely only to be effective if it prevents these births. Even though the individual morbidity and mortality is greater for very and extremely preterm infants, the sheer volume of later preterm births still carries a large health and socio-economic burden.

Effective interventions aimed at reducing spontaneous preterm labour and preterm rupture of membranes are likely to be of value across the gestational age spectrum. Avoidance of non-medically indicated iatrogenic preterm birth is a strategy which has a greater role in the prevention of late preterm and early term birth [20]. Holland et al. suggested in 2009 that 17% of late preterm births were potentially avoidable and that 8% were purely elective, providing evidence for this as a potential simple target for rapid reduction [21].

In response to an increasing rate of non-medically indicated late preterm and early term birth in the USA, programs were instituted to encourage physicians to avoid such obstetric intervention [22]. Three approaches were investigated: (i) a "hard-stop" approach, where policy was implemented prohibiting purely elective deliveries before 39 weeks; (ii) a "soft-stop" approach, where policy was introduced to avoid such deliveries but the decision was ultimately made by the attending physician; and (iii) an "education-only" approach, where information was provided about the potential harms of early term birth but no policy changes were made. In a pilot program in 27 hospitals broadly representative of the varied US demographic, where institutions were allowed to determine their own approach, elective early term delivery fell from 9.6% to 4.3% of all births [23]. Both hard-stop and soft-stop approaches resulted in significant reduction, while education-only was less effective. Hard-stop was associated with twice the reduction of soft-stop. Extrapolating from these data, a hard-stop approach to the entire USA was predicted to allow a potential reduction of 500,000 neonatal intensive care unit days per year at a cost saving of more than $1 billion. There was no significant change in the rate of stillbirth across these institutions during the study.

In the first published whole of population and whole of geographic region preterm birth prevention initiative, avoidance of non-medically indicated preterm birth prior to 38 weeks was one of several components aimed at reducing the rate of preterm birth across the state of Western Australia [24]. An education-only approach was employed, and an immediate reduction in early term births was observed, coupled with an increase in births at 39 weeks. This immediate result suggests that avoidance of non-medically indicated late preterm and early term birth was a significant contributor to an 8% reduction in preterm birth overall, as the other interventions were in early pregnancy and would have had a lead time to demonstrate their effects. No increase in stillbirth was seen, although a clinically significant increase or decrease could not have been excluded in this study of a population of 35,000 births per year.

4. Potential unintended adverse consequences

In 2009 the "39-week rule," where non-medically indicated delivery prior to 39 weeks was to be avoided, became a formal quality measure in the USA [25]. Subsequently, various clinical, administrative, and financial strategies were implemented to enforce adherence to this rule [26]. This was associated with a reduction in term births before 39 weeks in all jurisdictions. Of concern was that the rate of term stillbirth increased significantly across the study period from 1.103 to 1.177 per 1000 births. Whereas it is clear that a substantial reduction in early term births can be made, it is argued that this may have led to 335 additional stillbirths per annum as an unintended adverse consequence of the 39-week rule.

Concerns regarding a potential increase in stillbirth related to deferred early term birth should be weighed against other measures of improvement in perinatal and longer-term outcomes. Although meaningful long-term data are not yet available, a reduction in neonatal mortality during the same time-period as the previous study may be a benefit of the 39-week rule [27]. Furthermore, in their analysis of more than seven million term births in 2005 and 2011, Little and colleagues found no significant increase in stillbirth despite a 12% relative reduction in early term birth over the same period [28]. Similarly, the hard stop policy in Oregon saw a reduction in early term inductions and elective caesarean sections but no adverse effects on perinatal outcomes [29].

5. Challenges to the safe deferral of late preterm and early term birth

The potential for an increase in stillbirth with deferral of planned birth is a key limitation of interventions such as the 39-week rule. The challenge for clinicians is to identify those fetuses at risk of adverse perinatal outcomes who would do better from earlier delivery. Term stillbirths are uncommon, the tools that we currently employ to predict them are blunt, and our preventive strategies are limited to timely delivery. As such, a high false-positive rate is inherent in all current screening strategies for term stillbirth, and a large number of infants will be delivered early in order to prevent one stillbirth (Table 1) [30]. That is not to suggest that this is an unworthy goal, but we must be wary of unintended consequences of actions of noble intent, such as a significant population-level impact on neurodevelopmental outcomes from early birth.

Accurate prediction of term stillbirth and other adverse outcomes that may be prevented from earlier delivery will require a paradigm shift in the assessment of stillbirth risk. Traditional approaches based on maternal risk factors, fetal growth assessments, and ancillary ultrasound tools such as fetoplacental Doppler studies perform poorly for term outcomes compared to preterm outcomes [30–34]. Placental function biomarkers have not yet been clinically useful but are a

Table 1
Outcomes of elective delivery of all pregnancies at 37 or 38 weeks as a strategy to prevent term stillbirth.

Outcome	37 weeks			38 weeks			Reference
	Absolute risk change	No. needed to treat	Additional cases per stillbirth prevented	Absolute risk change	No. needed to treat	Additional cases per stillbirth prevented	
Stillbirth	0.18% reduction	553 (benefit)	–	0.12% reduction	819 (benefit)	–	[38]
Requirement for special educational assistance	1.8% increase	57 (harm)	10	1.0% increase	103 (harm)	8	[10]
Reading impairment	1.4% increase	71 (harm)	8	0.8% increase	125 (harm)	7	[12]
Developmentally high risk:							
Any domain	1.8% increase	42 (harm)	13	0.6% increase	167 (harm)	5	[16]
Physical health and wellbeing	2.7% increase	37 (harm)	15	0.8% increase	125 (harm)	7	[16]
Basic numeracy	2.2% increase	45 (harm)	12	0.2% increase	500 (harm)	2	[16]
Externalising behaviour problem	6% increase	17 (harm)	33	0.8% increase	125 (harm)	7	[14]

potential source of benefit in the future [35–37]. Regardless of the tools ultimately employed, an individualised assessment of fetal risk will be required to more precisely stratify risk such that early delivery, with its known short- and long-term adverse consequences, can be instituted only in those for whom the risk of deferred delivery is greater.

6. Conclusion

Late preterm and early term birth is associated with a significant increase in adverse short- and long-term offspring outcomes. Deferral of such births can be achieved by avoidance of non-medically indicated delivery prior to 39 weeks as demonstrated by programs such as the 39-week rule. The benefit of such interventions must be weighed against the potential for stillbirth associated with prolonging gestation, although recent studies from the USA are more reassuring than initial data suggested. A key future challenge is the development of tools to better identify the at-risk fetus for whom early planned delivery could be life-saving and the fetus whose birth it is safe to defer in the interest of improved perinatal and long-term outcomes.

6.1. Practice points

- Late preterm and early term birth is associated with adverse short- and long-term outcomes for the offspring, particularly in neurodevelopment.
- Obstetric intervention is a major contributor to such births and strategies to prevent non-medically indicated interventions have been effective in reducing their rate.
- Deferring late preterm and early term birth has the potential to increase stillbirth in those pregnancies.
- Balancing the benefits of full-term birth against the risk of late stillbirth is a key challenge for contemporary maternity care.

6.2. Research directions

- Assessing the true effect of deferred late preterm and early term birth on perinatal mortality.
- Developing tools to accurately stratify full-term perinatal mortality risk to guide obstetric intervention.

Conflicts of interest

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