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Maternal age and body mass index at term: Risk factors for requiring an induced labour for a late-term pregnancy

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ABSTRACT

Introduction: We investigated the role of body mass index (BMI) and maternal age on the risk of late-term induction, prolonged induction time and caesarean section (CS) after induction.
Material and Methods: This is a retrospective, observational study. All women without any fetal or maternal pathological condition, uterine scars or any other indication for an elective caesarean birth and had a singleton foetus in the cephalic position at term were included.
Results: A total of 4006 women had a spontaneous onset of labour and 612 were induced for a late-term pregnancy. Labour induction was significantly more common in overweight (Adj Odds Ratio (OR) 1.48 95%CI 1.22–1.78) and obese (Adj OR 1.63 95%CI 1.24–2.14) women. Among induced women, a BMI ≥ 30 was a risk factor for a prolonged induction time in both nulliparous (AdjOR 2.4, 95%CI 1.02–5.67) and multiparous women (AdjOR 4.24, 95%CI 1.02–17.6). A BMI > 25–29.9 was significantly associated with a prolonged induction time only in nulliparous women (AdjOR 1.86 95%CI 1.05–3.30). A CS was more frequent in overweight (AdjOR 1.74, 95% CI 1.052.89) and obese women (AdjOR 2.72, 95%CI 1.42–5.25). Nulliparous women ageed 30–34 years had an induction time longer than women <30 years (OR 2.04 95% CI 1.07–3.91).
Conclusions: The results of this study suggest that a BMI > 25 kg/m2 at term of pregnancy is a risk factor for the induction of labour during a late-term pregnancy, a prolonged induction time and higher caesarean section rate.

Key message

A body mass index at term >25 kg/m2 (an easily available data) is a significant determinat risk factor of an higher risk of indiced labour for a late term pregnancy, prolonged induction time and of caesarean section.

Introduction

In Europe, labour induction rates range from 7% to 33.0% [1]. Based on international recommendations [2], one of the main indications for the induction of labour is a late-term pregnancy, defined as delivery at 41 + 0–41 + 6 weeks of gestation [3]. This policy has reduced perinatal morbidity and mortality, as demonstrated in both systematic reviews of clinical trials [4] and nationwide following the introduction of protocols designed to induce late-term instead of post-term [5]. It is recognized that increasing gestational age increases the risk of neonatal and maternal complications, such as intrauterine foetal death, caesarean section, and postpartum haemorrhage [6]. This late-term induction policy did not increase the rate of caesarean sections [4].

This prudent policy has recently been challenged by large epidemiological cohort studies on selected low risk pregnancies [7] that recommend inducing women older than 35 years at 40 + 0. Limitations of these studies include the absence of any clinical data on the impact of late intrauterine growth restriction (IUGR), large for gestational age LGA, obesity, and poor management of late PE on perinatal death. In addition to this, the reported perinatal death rate of these normal foetuses at term was as high as 5/1000, 3/1000

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of which occurred in the hospital. As such, these figures are too high to be comparable with the perinatal outcomes observed in most western European countries [1].

Another area of investigation focuses on factors associated with a prolonged pregnancy that may contribute to a greater need for the induction of labour and its success. Maternal characteristics, such as obesity and an advanced maternal age play an important role [7]. The prevalence of overweight and obese patients, defined as body mass indices (BMI) of 25–29.9 and >30, respectively, has risen in recent years and can be considered pandemic in many countries [8]. Obesity during pregnancy is associated with a wide spectrum of adverse outcomes, including an increased rate of caesarean section (CS), postpartum haemorrhage, and higher risks of maternal hypertension, gestational diabetes and foetal death [9]. There is also a strong association between obesity and the risk of post-term delivery, and a higher maternal BMI is associated with a decreased likelihood of the spontaneous onset of labour [10], requiring an induction more often [11].

In particular it has been suggested that overweight and obesity affect labour and responce to induction [12–14] Over the past few decades, a continuous increase in maternal age at birth has been observed [15]. Advanced maternal age has been connected to prolonged pregnancies [16], failed inductions [17] and higher rate of CS following the induction of labour [18]. It has also been shown that older women are more likely to experience a prolonged labour than younger women [19].

Available data on the relationship between maternal BMI and delivery outcome are mostly based on North American populations which are characterized by a high prevalence of overweight. Thus iit s of interest to analyze this relation in different populations and particularly in South European countries, characterized by different dietary pattern and prevalence of overweight.

The aim of this study is to investigate the impact of maternal age and BMI on the risk of a late-term induction, a prolonged induction time and the need for CS after induction.

Methods

This was a retrospective, observational study based on women who delivered at the Obstetric Unit, Buzzi Children's Hospital, Biomedical and Clinical Sciences School of Medicine, University of Milan between January 2014 and June 2016. The institutional review board according to Italian law and privacy regulations approved the study (register number of opinions: 120-022015). Despite the retrospective nature of this analysis, all demographic data, clinical variables and perinatal outcomes were recorded into a dedicated on-line computerized database each time the woman and her baby were transferred from labour and delivery to puerperium.

The study included all women who delivered a singleton foetus in cephalic presentation at or beyond early term following the spontaneous onset of labour, with a late-term pregnancy as the only indication for the induction of labour.

Exclusion criteria were: complications of pregnancy (hypertensive disorders of pregnancy, gestational diabetes, a previous admission for threatened preterm labour, and a uterine scar or any indication for an elective caesarean birth), foetal growth restriction according to the consensus reported in the Delphi criteria [20], and foetal anomalies.

Maternal characteristics, such as origin, age, height, weight, gestational age, parity, and mode of conception were recorded at admission with a dedicated Clinical Record Form.

Maternal BMI (kg/m^2) was calculated from maternal weight and height measurements at admission, and stratified into categories proposed by the WHO in 2006 [21]: underweight (<20 kg/m^2), normal (20 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (30 to <35 kg/m^2 class obesity I; 35 to <40 kg/m^2 class II obesity and BMI ≥40 kg/m^2 class III obesity).

All women were weighed when admitted for labour. Women with BMI value missing are not included (Fig. 1).

Gestational age was assessed on ultrasound during the first trimester as per the standard of NHS care in Italy. Foetal growth was routinely assessed at 20–22 weeks of gestation, at 28–32 weeks of gestation as per Italian guidelines, and at 37–39 weeks by symphysis fundal length and foetal abdominal biometry was performed if this screening measure was outside the interquartile range, or in all pregnant women with a term BMI > 30.

Induction for a late term pregnancy was routinely performed between 41 + 3 and 41 + 5 weeks + days.

The presented analysis considers only women induced for late term pregnancy. Women with missing values for age or BMI were excluded. Likewise fetal deah are not included. (Fig. 1)

No methods of labor pre-induction were applied. Capsules containing 25 mcg of misoprostol were prepared by the hospital pharmacy and administered sublingually every 4 h until active labor was achieved up to a maximum of 12 doses. Cardiotocography (CTG) was performed for at least 20 min before and 50 min after administration of misoprostol. Active labor was diagnosed as three or more contractions in 10 min and cervical dilatation greater than 3–4 cm were recorded. CTG was performed continuously during labor. Neither artificial rupture of the membranes nor oxytocin administration was carried out routinely. Amniorexis and oxytocin administration were performed during labor if dilatation did not progress after 2 h of regular uterine contractions. Cesarean section was performed for failure to progress if progression of dilatation was not obtained after 6 h of oxytocin administration.

If labor was not achieved after administration of 12 doses of misoprostol, further treatments were discussed with the patient: when Bishop score was equal or more than 6, oxytocin administration was proposed; when cervix was still unfavorable (Bishop score <6), women were offered the option to proceed with induction of labor (either by sublingual misoprostol or by vaginal prostaglandin E2) or to deliver by cesarean section. After the first 12 doses, a day of rest was allowed if requested by the patient and maternal fetal conditions posed no contraindications. Epidural analgesia was available on request to all patients in active labor [22].

Our primary outcome was the effect of BMI and maternal age on the outcome of a late-term induction of labour. Our secondary outcome was an estimate of how BMI and maternal age might influence the risk of a prolonged induction time and caesarean section after induction.

Statistics

Descriptive statistics of patient characteristics were reported separately based on if labour was spontaneous or induced and were presented as a whole series, separately between nulliparous and multiparous women, and according to duration of induction and outcome of the procedure.

An unconditional simple and multiple (including age, BMI, origin, mode of conception, parity) logistic regression model was performed to estimate unadjusted and adjusted odds ratios (ORs) and relative 95% confidence intervals (95% CI), with the aim of identifying potential risk factors for labour induction, the duration of the induction, and the need for a caesarean section among women with a late-term induced labour.

In the cohort of women who underwent a labour induction, the duration of the induction was defined as the time from initial drug administration to the onset of labour. The duration of the induction was stratified into three groups: short induction times were less

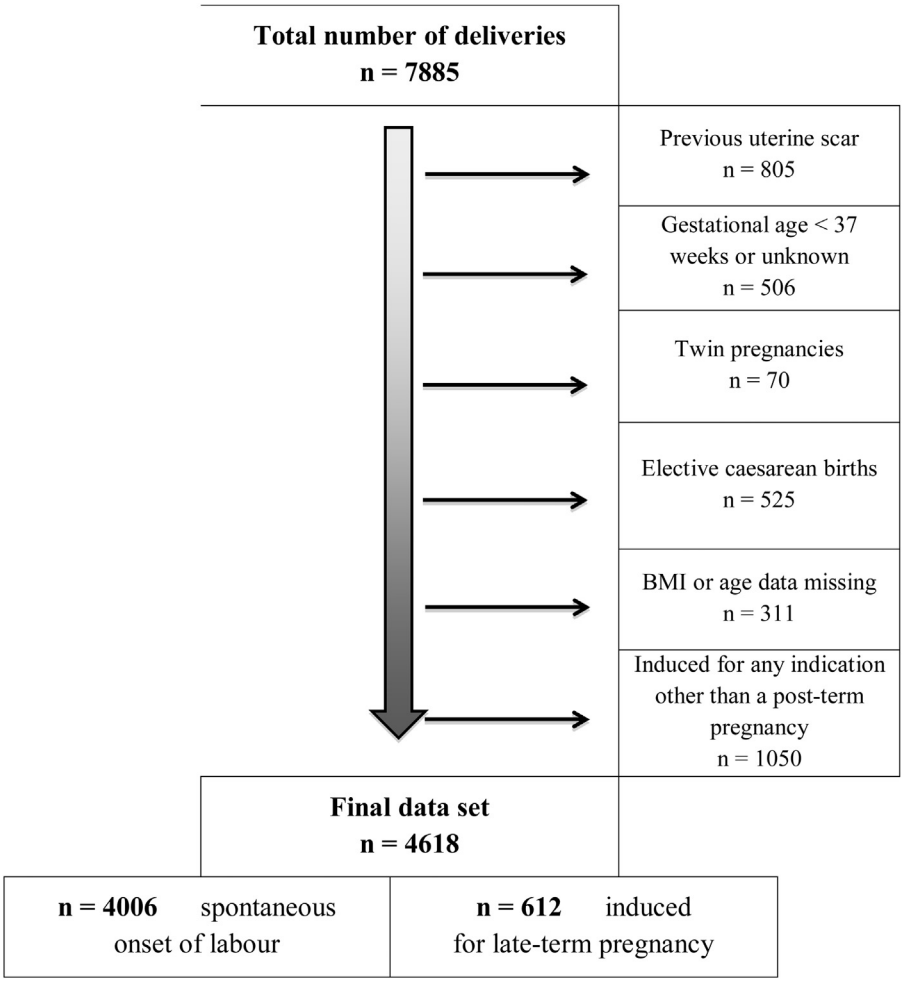

Fig. 1. Flow chart of the study.

than or equal 12 h, a medium induction time was between 13 and 24 h, and a prolonged induction time was more than 24 h.

The time to vaginal delivery was evaluated using log-rank tests with the survivor function calculated using the Kaplan-Meier estimator. Time-to-event analyses were based on the initial induction attempt.

Women who had cesarean deliveries or did not deliver after the first induction attempt were censored in the time-to-event analyses using times that equaled the longest time to cesarean delivery or longest time to discharge from the labor and delivery suite of any participant in the study independent of treatment group, respectively [23].

Results

A total of 7885 deliveries took place at our unit during the study period.

After a selection based on our exclusion criteria, we analysed a total of 4618 pregnant women: 4006 had a spontaneous onset of labour, and 612 were induced solely for a late-term pregnancy (Fig. 1).

Table 1 shows the characteristics of this cohort, stratified by the spontaneous or induced onset of labour. The prevalence of induced labour was significantly higher in overweight and obese women (Fig. 2a). The risk of induction increased with increasing BMI, and remained significant when adjusted for parity. No significant relationship was observed between induction rate and maternal age or mode of conception.

Table 2a and 2b show the results of logistic regression models that were computed to analyse the effects of maternal BMI and age on the duration of induction in nulliparous and multiparous women. A BMI > 30 compared to a BMI of 20–24.9 was a risk factor for a prolonged induction time both in nulliparous and multiparous women. Being overweight (BMI 25–29.9) was significantly associated with a prolonged induction time only in nulliparous women. Maternal age was associated with a longer induction time only in 30–34-year-old nulliparous women.

Time to event analysis largely confirm these findings (Fig. 3)

With respect to the mode of delivery in induced women, the risk of caesarean section increased with increasing BMI among overweight (Adjusted OR 1.74 95%CI 1.05–2.89) and obese women (Adjusted OR 2.72; 95% CI 1.42–5.25) (Fig. 2b). As expected, the caesarean section rate was significantly lower in multiparous women (Adjusted OR 0.12; 95%CI 0.06-0.28). We observed a significantly higher risk of a caesarean section after induction (Adjusted OR 2.39 95%CI 1.28-4.45) in non-Caucasian women of southern European ancestry. No significant association was observed between mode of delivery and maternal age.

We also analysed the risk of caesarean sections indicated for foetal distress: neither BMI nor age were significantly associated with a higher caesarean section rate for foetal indications (overweight women: Adjusted OR 0.82 95% CI 0.3–2.23; obese women: Adjusted OR 1.31 95%CI 0.37–4.65; 30–34 years; old women: Adjusted OR 0.64 95%CI 0.23–1.84 for; >35 years old women: Adjusted OR 1.78 95%CI 0.54–5.85).

Table 1
Study subject characteristics grouped by spontaneous onset or induced labour.

	Labour			Multiple logistic regression		
	Spontaneous	Induced		OR[a]	95%CI	
Variables	N	N	row%			
	4006	612	13.3			
Gestational age at delivery						
Median (IQR)	39^{+6} (39^{+0}-40^{+3})	40^{+3} (39^{+2}-41^{+3})				
$\leq 37^{+0-6}$	88	–				
38^{+0-6}-40^{+0-6}	1533	357				
$\geq 41^{+0-6}$	227	281				
Age (year)						
<30	979	145	12.9	1+		
30-34	1416	216	13.2	0.99	0.78	1.26
35-39	1259	193	13.3	1.12	0.88	1.44
40+	352	58	14.2	1.17	0.82	1.66
BMI						
≤19.9	107	8	7.0	0.62	0.30	1.29
20–24.9	1723	211	10.9	1+		
25–29.9	1708	304	15.1	**1.48**	**1.22**	**1.78**
30–34.9	385	65	14.4	**1.43**	**1.06**	**1.95**
35–34.9	74	20	21.3	**2.57**[a]	**1.58**	**4.20**
40+	9	4	30.8	–	–	–
Country of family origin						
Italy	3142	531	14.5	1+		
Sino-Asian countries	388	26	6.3	**0.44**	**0.29**	**0.67**
South America	224	24	9.7	0.65	0.42	1.01
Middle east	127	13	9.3	0.67	0.37	1.20
Sub-Sahara countries	65	8	11.0	0.81	0.38	1.73
Missing	60	10	14.3	0.90	0.45	1.79
Conception						
Spontaneous	3754	558	12.9	1+		
Assisted	112	27	19.4	1.17	0.74	1.83
Missing	140	27	16.2	1.26	0.82	1.93

[a] In the multiple logistic regression model the 2 categories 35–39.9 and 40+ have been joined. The OR and relative 95% confidence interval estimate the risk of the women with BMI ≥ 35 versus BMI between 20 and 24.9. All the variable presented in the table have been included in the multiple logistic regression model (age and BMI are included).

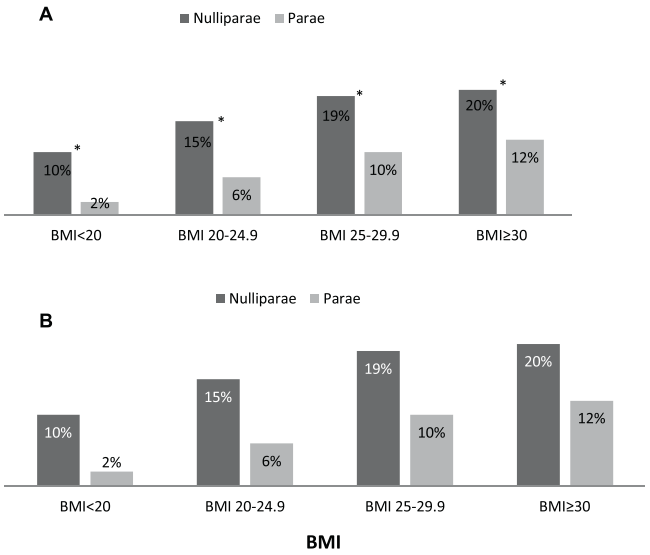

Fig. 2. a. Percentage of women who underwent an induction of labour for a late-term pregnancy, stratified for BMI class and parity. *Nulliparae vs parae: P < 0.05. The trend in risk of induction of labour for a late-term pregnancy with increasing BMI was statistically significant in nulliparare (p = 0.03) and in parae (p < 0.001) b. Percentage of women who underwent a Cesarean section after induction of labour for a late-term pregnancy, stratified for BMI class and parity. *Nulliparae vs parae: P < 0.05. The trend in risk of caesarean section after induction of labour for a late-term pregnancy with increasing BMI was statistically significant in nulliparare (p = 0.01).

Discussion

Main results

The main result of our study is that being obese or just overweight at term is a risk factor for non-spontaneous labour in a late-term pregnancy in both nulliparous and multiparous women These data support previous findings from different populations [24–29].

Increased maternal age tended to be associated with a longer duration of induction in nulliparous women, but the association was significant only in women 30–34 years old and not in women >35.

Secondary findings of our study were a significant association between increased maternal BMI, prolonged induction times and an increased risk of a caesarean section, which was not observed with increased maternal age. The caesarean section rate for foetal indications was not associated with increased BMI or maternal age.

Interpretation of results

The impact of obesity on a prolonged pregnancy has already been reported by large epidemiological surveys of 20 thousand deliveries. A prolonged pregnancy (>41 + 3 weeks + days) was significantly more common in obese women than in normal weight women (30% versus 22.3%). Among the 3076 women who underwent an induced labour, a significantly increased caesarean section rate was observed in obese women versus those with a normal weight (28% versus 18%) [30]. Similar findings were

Table 2a
Multiple logistic regression on the duration of induction in nulliparous women.

	≤12 hours		13–24 hours					>24 hours				
	N=163	%	N=147	%	OR	95%CI		N=104	%	OR	95%CI	
Age												
<30	50	30.7	39	26.5	1+			26	25.0	1+		
30-34	55	33.7	56	38.1	1.32	0.74	2.37	48	46.2	2.04	1.07	3.91
35+*	58	35.6	52	35.4	1.13	0.63	2.03	30	28.8	1.25	0.64	2.48
BMI												
<20	1	0.6	4	2.7	NE			1	1.0	NE		
20-24.9	62	38.0	63	42.9	1+			25	24.0	1+		
25-29.9	84	51.5	57	38.8	0.66	0.41	1.08	63	60.6	1.86	1.05	3.30
30+	16	9.8	23	15.6	1.50	0.72	3.13	15	14.4	2.40	1.02	5.67
Origin												
Caucasian	146	89.6	134	91.2	1+			88	84.6	1+		
Other	15	9.2	11	7.5	0.76	0.34	1.70	13	12.5	1.83	0.84	3.99
Missing	2	1.2	2	1.4	NE			3	2.9	NE		

*Age, BMI (in turn) gestational age (<41 vs > = 41) and Origin included in the model. Origin and conception were excluded because of non significant values in univariate analysis and low numbers in some categories.
**The category age≥40 years of the frequency table was joined with the category 35–39 years.
NE = not evaluable due to low numbers.

Table 2b
Multiple logistic regression of the duration of induction in multiparous women.

	≤12 hours		13–24 hours					>24 vs				
	N=87	%	N=43	%	OR	95%CI		N=26	%	OR	95%CI	
Age												
<30	12	13.8	9	20.9	1+			2	7.7	1+		
30–34	18	20.7	16	37.2	1.36	0.43	4.24	10	38.5	4.28	0.75	24.62
35+*	57	65,5	18	41.9	0.52	0.17	1.61	14	53.8	2.15	0.37	12.34
BMI												
<20	1	1.1	0	–	NE			0	–	NE		
20-24	32	36.8	10	23.3	1+			4	15.4	1+		
25-29.9	39	44.8	26	60.5	2.20	0.90	5.35	15	57.7	3.22	0.95	10.97
30+	15	17.2	7	16.3	1.82	0.56	5.91	7	26.9	4.24	1.02	17.60
Origin												
Caucasian	75	86.2	32	74.4	1+			19	73.1	1+		
Other	12	13.8	10	23.3	1.64	0.58	4.63	7	26.9	2.65	0.79	8.90
Missing	0	–	1	2.3	NE			0	–	NE		

*Age, BMI (in turn) gestational age (<41 vs > = 41) and Origin included in the model. Origin and conception were excluded because of non significant values in univariate analysis and low numbers in some categories.
**The category age≥40 years of the frequency table was joined with the category 35–39 years.
NE = not evaluable due to low numbers.

observed in population-based cohorts [16]. In a large one million patient study [16], obese women had a higher risk of a post-term pregnancy (≥42.0 weeks) (adj OR 1.63, CI 1.59–1.67) and twice the normal risk of CS following an induced labour (adj OR 1.87, CI 1.71–2.04). Unfortunately, obstetrical complications were not excluded in these large cohorts. In this latter study, maternal age was significantly correlated with a post-term pregnancy. We did not observe any significant association between maternal age and the rate of induction at 41 + 3 weeks + days of gestation. This might be the result of the exclusion of pregnancy complications that are more frequently associated with an advanced maternal age, such as late IUGR or gestational diabetes. We only observed that nulliparous women 30–34 years old had a longer induction time than younger women. In our study, age did not influence the rate of caesarean sections. Prior studies have reported an increased risk of a prolonged pregnancy and CS after induction with a maternal age greater than 30 years [16,30].

In a larger retrospective cohort study of 7459 women, a multivariate logistic regression analysis adjusted for 11 covariates showed that advanced maternal age was independently associated with an increase in CS following labour induction in pregnant women >35 years (OR 2.01 95%CI 1.58–2.57), and for pregnant women >40 years (OR 3.17 95%CI 2.01–5.01) [18]. Maternal age is a key issue given the trend towards an increased maternal age at first delivery. Walker et al. performed a randomized trial that proved their hypothesis that labour induction in women older than 35 years at 39 weeks of gestation had no effect on the rate of caesarean sections, and no short-term adverse effects on maternal or neonatal outcomes [31].

The BMI classes in our study were based on term weight. We purposely adopted this criteria since excess gestational weight gain causes an increase in pro-inflammatory mediators in the maternal blood, such as PCR, SSA, and IL-8, which is a condition that is also associated with increased total body water [32].

Obesity is metabolic dysfunction that is associated with a high risk of low grade inflammation. In pregnancy, this means a reduction in placental corticotrophin-releasing hormone production [33]. These factors in obese women at term might alter the inflammatory balance necessary for normal parturition. In humans, labour is associated with a functional withdrawal of progesterone, not a real placental decrease as in other mammals, which is achieved by an overexpression of decoy progesterone receptors-A that block progesterone's effects on active receptors-B [34]. In addition to this, oestrogen and oxytocin receptors are located on the myometrial cell in caveolae, which are down-modulated by high cholesterol levels. We know that the immune

	Unudjusted HR			Adjusted HR		
Age (yrs)	**p-value**	**Hazard Ratio**	**95%CI**	**p-value**	**Hazard Ratio**	**95%CI**
<30		1*			1*	
30-34	0.6865	0.95	0.8-1.2	0.5312	0.93	0.7-1.2
35-39	0.1653	1.19	0.93-1.5	0.2393	1.16	0.9-1.5
40+	0.8900	1.03	0.7-1.4	0.9667	1.01	0.7-1.4
BMI						
<20		1*				
20-24.9	0.6370	0.83	04-1.8	0.5526	0.80	0.4-1.7
25.29.9	0.2578	0.65	0.3-1.4	0.2215	0.62	0.3-1.3
30+	0.1547	0.57	0.3-1.2	0.1223	0.54	0.2-1.2
Origin						
Caucasian		1*				
Other	0.1929	0.83	0.6-1.1	0.2591	0.85	0.6-1.1

*Reference category

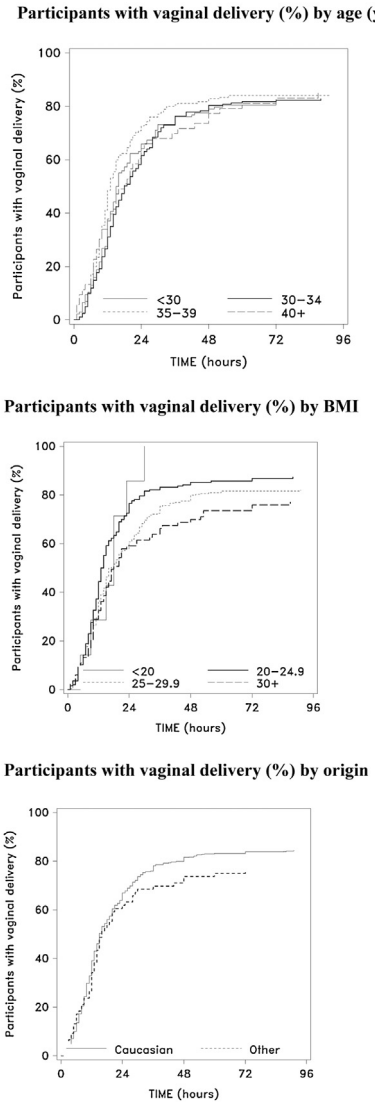

Fig. 3. Results of the COX univariate and multivariate (including term in turn for age, BMI and origin) regression analysis for time toevent analysis.

cross-talk between maternal monocyte (CD14) and monocyte derived macrophages that infiltrate the placenta is altered in obese women, in whom up to 90% of placental monocytes are of maternal origin and create a higher degree of inflammation [35]. Based on this biologic evidence, we might speculate that obese women as well as those who gain excess weight during pregnancy have a profoundly reduced response of their myometrium to the normal cascade of parturition. Indeed, this remains an area of future research that might help to identify better induction strategies for obese women, beyond the use of prostaglandins to overstimulate their myometrial cell.

Concerning the prolonged induction time, increased failed induction rate, and worse myometrial receptor activity observed in obese women [34], we must also to take into account the pharmacokinetics and pharmacodynamics of prostaglandins. The relative increase in the volume of distribution in obese women has a dilution effect that results in a reduced tissue concentration of the active molecule.

Strength and limitation

The strength of our findings derives from a focused analysis on a homogenous subset of women who were induced only for late term pregnancy. We have excluded from the analysis induced women for any other indications. In our opinion this design offers the opportunity of analyze the role of age and BMI on the outcome of induction in late term pregnancies, without any bias due to the inclusion of women with fetal or maternal pathological conditions. For this reason, the higher rates of induction observed among overweight women could not be attributed to a higher likelihood of pregnancy-related complications in obese women. However, the relatively small number of cases limits the strength of our study, in particular it make impossible to perform analysis on BMI > 35 or >40. The same goes for advanced maternal age, e.g. > 35 years old or >40 years old.

Pre pregnancy BMI is generally considered in the studies on the relation between BMI and delivery. Our study was based on a database of women admitted at delivery room, thus only weight at term was available. This a limitation of this study. However we can consider that weight at term may be a proxy of pre pregnancy weight. Another potential bias is also due to the fact that pregnancy in the late term group is longer than in women with spontaneous labour, thus an additional weight gain can be expected in this group.

In the interpretation of the results of this study it should also be considered their generalizability. In particular the 9% of considered women aged 40 years or more.

To analyze the determinants of induced labour we have compared spontaneous term women with induced late term. This comparison may have introduced some bias. Theoretically, It should be better to compare spontaneous late-term women with induced late-term women. However, in consideration of the observational design of this analysis, we have no case of spontaneous late-term birth, since in our hospital all women are induced at late term.

In conclusion, the results of this study suggest that a BMI > 25 kg/m2 at term is a significant risk factor for requiring an induced labour for a late-term pregnancy, a prolonged induction time and a significantly higher caesarean section rate.

The recognition of this risk factor has both preventive and therapeutic implications. Nutrition and exercise should be recommended and endorsed with positive ongoing counselling to prevent an excessive weight gain during pregnancy. With regard to therapy, a BMI > 30 should be considered an indication for appropriate prostaglandin dosing or for a more liberal use of mechanical devices for cervical effacement to avoid prolonged prostaglandin use.

These results confirm that overweight and obese women are less likely to start labour spontaneously and, as shown by previous studies, are at a greater risk of developing post-term related complications. These fnding potentally suggest that induction of

labour for late-term pregnancies in overweight and obese women should be encouraged: A clinical RCT on induction of labour at certain GA versus expectant management is or observational studies in a large population could be beneficial.

Conflicts of interest statement

No conflict of interest to declare by all the Authors.

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