Trends and regional variations in prescriptions dispensed to stimulate uterine contractions at the end of pregnancy in Belgium: a community-based study from 2003 to 2018

Running title: Peripartum uterotonics prescribed in Belgium

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Abstract

Purpose: To investigate the trends and regional variations in uterotonics dispensed around birth between 2003 and 2018 in Belgium.

Methods: Data, including outpatient and inpatient prescriptions were extracted from a nationally representative prescription database. The prevalence of uterotonics dispensed during a period including the 7 days before birth, the delivery day and the 7 days after birth was computed over three 4-year-long study periods from 2003 to 2018. The trends between periods and associations between the use of at least one uterotonic and maternal age, region of residence, delivery type and social status were assessed using logistic regression.

Results: In total, 31,675 pregnancies were included in the study. The proportion of pregnancies exposed to at least one uterotonic decreased significantly from 92.9% (95%CI, 92.3-93.4) in 2003–2006 to 91.4% (95%CI, 90.7-92.0) in 2015-2018 for vaginal births and from 95.5% (95%CI, 94.5-96.4) to 93.7% (95%CI, 92.6-94.7) for caesarean sections. However, for vaginal births, the proportion of oxytocin increased from 84.5% (95%CI, 83.7-85.2) to 89% (95%CI 88.3-89.7). A significant association was found between uterotonic agent use and maternal age, region of residence, and delivery type. The dispensation of some uterotonic agents differed significantly between the regions.

Conclusions: The proportion of pregnancies exposed to at least one uterotonic was high across the study period but decreased slightly between 2003 and 2018. Important variations in uterotonic use between regions highlight the need for improved national guidance.

Keywords: administrative healthcare database, pregnancy, uterotonic, labour, induction, augmentation, post-partum haemorrhage

Plain Language Summary:

This study investigated the trends and regional variations in uterotonics dispensed around birth between 2003 and 2018 in Belgium. Most pregnancies in Belgium involve exposure to at least one uterotonic around birth. Between 2003 and 2018, the proportion of pregnancies exposed to at least one uterotonic slightly decreased, suggesting a trend favoring a less medicalized birth experience in

Belgium. However, the use of some uterotonics has increased, as has oxytocin and misoprostol use in vaginal birth. We also observed significant differences in the proportion of pregnancies exposed to different uterotonics across the three regions of Belgium, emphasizing the need for uniform national guidelines.

Key Points:

- The proportion of pregnancies exposed to at least one uterotonic around birth decreased slightly between 2003 and 2018.
- The use of at least one uterotonic agent was associated with maternal age, region of residence, and delivery type.
- The off-label use of misoprostol in obstetrics increased significantly between 2003 and 2018.
- In the period (2015-2018), 89% of pregnancies were exposed to at least one oxytocin prescription for a vaginal birth.
- Important variations were observed between regions of uterotonic dispensation.

Introduction

In obstetrics, uterotonics are used in various situations, including abortion, labor induction, and the prevention and treatment of postpartum hemorrhage (PPH). Despite their benefits, uterotonics may also be associated with adverse events[1,2] such as tachycardia, high blood pressure, vomiting, and possibly impact breastfeeding rates.[3,4]A study conducted in Sweden has observed that among 1,267 pregnant women, the induction or augmentation of labor with oxytocin was used in 55% of pregnancies while the frequency of labor dystocia was 19.8%. Additionally, incorrect dosages of oxytocin were administered, with 7.3% of pregnant women receiving a higher dose and 42.6% a lower dose than the one recommended by guidance.[5] Therefore, monitoring their use is important and can play a role in correcting uterotonic prescription habits in obstetrics.

The risk-benefit balance is different when uterotonic agents are used before delivery to induce and augment uterine contractions than when used after birth to prevent and treat PPH associated with

uterine atony. Induction and augmentation of labor often involve the use of uterotonics. The World Health Organization (WHO) recommends the induction of labor for women who are known to have reached 41 weeks of gestation.[6] Although uterotonics have long been known to effectively induce or augment labor,[7-9] their safety still cannot be guaranteed. Some studies have reported an association between the use of uterotonics and a higher risk of PPH[10-12] and an increased risk of stillbirth and neonatal asphyxia.[13] They should only be used when continuing pregnancy involves more risks than uterotonic use.[6] Uterotonics are also used in the third stage of labor to prevent or treat PPH after vaginal birth (VB) or caesarean section (CS). PPH is an important cause of maternal death.[14] Most guidelines promote the administration of uterotonics immediately after birth[15-19] as part of "the active management" of the third stage of labor, including cord clamping and controlled cord traction to help deliver the placenta. Although active management reduces maternal blood loss at birth,[20] it may also increase maternal diastolic blood pressure, postpartum vomiting, postpartum pain, and hospital readmission due to bleeding.[20]

In other countries, studies using large databases or billing data to evaluate the use of uterotonics are scarce because such databases often do not capture medications used in hospitals.[21-23] In Belgium, inpatient medications are recorded; therefore, Belgian data represent an opportunity to highlight practices in real-world contextual settings. The present study explored at national and regional level the trends and prescribing pattern of uterotonics dispensed around birth in Belgium. More specifically, we assessed the period of exposure in the seven days preceding childbirth, the day of childbirth and seven days after childbirth.

Methods:

Study design and data source

This was a retrospective drug utilization study. Data were extracted from the permanent sample (EPS). In Belgium, health insurance is mandatory, 98% of residents are captured. The EPS

database is a 2.5% representative sample constituted by the Inter Mutualistic Agency with the information received by all insurance funds. The information is collected by patient and includes a pseudonymised unique patient identifier, demographic characteristics such as patient's age and residence region. The social status can also be identified because patients with low-income benefit from a preferential reimbursement rate. Medications prescribed and dispensed from community and hospital pharmacies were captured. In community pharmacies, only reimbursed medications were registered. For hospital pharmacies, all medications including non-reimbursed medications prescribed and dispensed during hospitalization were captured even for a day-care stay at the hospital or in ambulatory care. Additionally, the medication received when the patient left the hospital was also recorded. Information collected on medication includes classification according to the Anatomical Therapeutic Chemical Classification Code (ATC), the exact date of dispensation, and the quantity dispensed. All information was completely anonymized and accessible for research purposes under strict conditions. [24]

Study periods

To examine the evolution in the prescriptions of uterotonics dispensed around birth, we established three study periods of four years each between 2003 and 2018: (2003–2006) (2009–2012) (2015–2018).

Study population

This analysis only considered women who gave birth. Reimbursement delivery-only codes were used to select women from the EPS. The selection of codes only included deliveries that occurred after the 180th day of pregnancy.[25] Mothers whose data were not available in the EPS for the entire pregnancy period and those whose residences were outside Belgium were excluded. Finally, we excluded self-employed mothers who did not benefit from the same reimbursement scheme for drugs during the first study period (2003–2006) for all three periods.

Definition of exposure and measurement

We identified all ATC codes associated with a uterotonic used to induce labor or to prevent or treat PPH commercialized in Belgium during the study period: dinoprostone (ATC: G02AD02), carboprost (ATC: G02AD04), methylergometrine (ATC: G02AB01), oxytocin (ATC: H01BB02), carbetocin (ATC: H01BB03), and misoprostol (ATC: A02BB01-G02AD06). The list is presented in Supplementary Table S1. We did not include mifepristone (ATC: G03XB01) because this medication is mainly used to manage miscarriages and fetal death. We considered the period of exposure to seven days preceding childbirth, the day of childbirth, and seven days after childbirth, as uterotonics might be prescribed and dispensed before, during, and after delivery.

Statistical methods

For the three study periods, the proportion and 95% confidence intervals of pregnancies exposed to at least one uterotonic from the pre-established list and for each individual uterotonic were computed. We also computed the proportion of pregnancies exposed to at least two and three distinct subgroups of uterotonics (different ATC codes at the 5^{th} level). The results are presented separately for the VB and CS. Logistic regression analysis was used to assess the trends in the proportion of pregnancies exposed to uterotonics across the three study periods, adjusted for maternal age.

For the last study period, we computed the adjusted odds ratio using logistic regression to measure the strength of the association between the proportion of pregnancies exposed to at least one uterotonic agent and maternal age, region of residence, delivery type, and social status.

Additionally, to explore regional disparities in the proportion of pregnancies exposed to different uterotonics, we assessed the proportions by region and presented the results separately for VB and CS. We determined significant differences between regions after adjusting for maternal age using logistic regression analysis.

Results

This study included 31,675 pregnancies during the three study periods (Figure 1). Table 1 shows the proportion of maternal age, region of residence of the mother, and delivery type.

In the period 2003–2006, the majority of mothers were in the age group 25–29 years while in the period 2015–2018 the majority were in the age group 30–34 years.

In the last study period, 19.1% of pregnant women benefited from a preferential reimbursement rate.

The prevalence of pregnancies exposed to at least one, two, or three subgroups of uterotonics (different ATC codes at the 5th level) dispensed around birth is shown in Table 2. Between 2003 and 2018, decreases in the use of at least one and two or more different uterotonics (from 92.9% to 91.4% and from 45.3% to 25.7%) were observed for VB. Similar significant decreases were observed for CS (from 95.5% to 93.7% and 38.8% to 29.9%) as well. The factors associated with pregnancies with exposure to at least one uterotonic agent are listed in Table 3. Maternal age, region of residence, and delivery type were statistically associated after adjustment. No association was found between social status and the use of at least one uterotonic.

The proportion of pregnancies exposed to at least one prescription for each uterotonic is listed in Table 4. For VB, the proportion of pregnancies exposed to oxytocin was high and increased significantly across the three study periods. In contrast, oxytocin use for CS decreased during the three study periods.

The proportion of pregnancies exposed to at least one prescription of different uterotonics during the three distinct periods around birth is listed in Table 5. The exposure period was divided into three distinct periods:7 days before delivery, the day of delivery, and 7 days after delivery. Most exposures occurred on the day of the delivery. Except for dinoprostone, pregnancies were exposed more frequently to each uterotonics seven days after delivery than seven days before delivery.

The geographical variations in uterotonics dispensed around delivery are listed in Table 6. For VB, the results reflected a higher prevalence of pregnancies exposed to oxytocin in Wallonia. The proportion of misoprostol use was slightly higher in Flanders than in Brussels but was much lower in Wallonia. For CS, carbetocin use was similar in Flanders and Wallonia but was significantly lower in the Brussels region.

Discussion

The proportion of pregnancies exposed to at least one uterotonic decreased slightly across the three study periods. For the proportion of pregnancies exposed to two, three, or more subgroups of uterotonics, the decrease was more significant, which might be explained by the increasing trend in the use of uterotonics that fit several indications, such as misoprostol and oxytocin. In addition, we hypothesized that an important part of the proportion of pregnancies with two or more different uterotonics would reflect induced deliveries. The decrease observed for this proportion might be related to the decrease in induced labor observed in Belgium from 32.1% in 2002 to 26.6% in 2015.[26]

Widely prescribed Oxytocin

In the last study period, 89% of VB were exposed to at least one prescription of oxytocin dispensed around birth. The widespread use of oxytocin for VB is based on WHO recommendations for PPH prevention. Although a very large consensus supports uterotonic use to prevent PPH[15,16,27], we observed 11% of VB not exposed to oxytocin and 8.6% of pregnancies not exposed to any uterotonics. Unexposed pregnancies may reflect, in part, the place of the “expectant management” in the third stage of labor in Belgium. Indeed, in addition to active management involving the systematic use of uterotonics, “expectant management” allows the placenta to be delivered spontaneously through maternal effort and gravity.[28]

The significant decrease observed in oxytocin use for CS was most likely related to the introduction of carbetocin (Pabal®) in Belgium in 2008. Our results suggest that carbetocin could

replace oxytocin to prevent PPH after CS. Similar results were observed in a study conducted in Canada.[21]

In the last study period, we examined prescriptions dispensed during three different exposure periods: (a) seven days before delivery, (b) day of delivery, and (c) seven days after delivery. This separation aimed to distinguish the uterotonics used to induce labor from those used to prevent or treat PPH. Oxytocin was the most represented uterotonic in the period before delivery and on the day of delivery, suggesting that it was the most commonly used uterotonic to induce or augment labor.

A drastic decrease in methylergometrine use

In Belgium, methylergometrine was commercialized only under the name Methergin®, and was largely used in the first study period (2003–2006). However, a drastic decrease was observed during the next two study periods. This is a consequence of several cases of accidental oral administration of Methergin® to the newborn because of confusion between the Methergin® dedicated to the mother and the paediatric preparation (often vitamin K) dedicated to the newborn.[29,30] Because of these incidents, drop preparations of Methergin® were withdrawn from the Belgian market in 2011.[31] Only intramuscular administration of Methergin® remained available. Our study suggests that for PPH prevention in VB, Methergin® has been replaced by oxytocin. For CS, our data suggest replacement of Methergin® with carbetocin.

The off-label Misoprostol use: an increasing trend

We observed an increasing trend in the misoprostol prescribed and dispensed around birth between 2003 and 2018. In Belgium, until 2016, misoprostol was only available under the Cytotec® formulation, which is not approved for use in obstetrics.[32] The increasing trend of Cytotec® use observed in our study may be explained by several factors. Many studies over the past two decades have suggested that misoprostol effectively induces labor and treats PPH.[8,33-35] Additionally, misoprostol is easy to store at room temperature, inexpensive, and has a short half-life.[35,36] The off-label use of misoprostol is controversial. In 2005 and 2013, the French National Agency for Medicine

issued warnings about the risks associated with Cytotec® use in obstetrics and gynaecology[37] and the drug was withdrawn from the French market in 2018.[38] More recently, in March 2020, the German Federal Institute for Drugs and Medical Devices was informed of new reports of severe side effects when using Cytotec® outside the approved indication.[39]

Geographical variation

Belgium is divided into three regions: Flanders, Wallonia, and Brussels. While the accessibility and reimbursement status of different uterotonics were the same across the country, we observed wide variations in their prescription patterns. Adjusted for maternal age, delivery type and social status our results found a statistically significant association between region of residence and higher odds of uterotonic dispensation. These variations may be explained by various factors.

First, important variations in obstetric practices between the regions of Belgium have influenced the use of uterotonics. For example, the proportion of induced deliveries varies significantly depending on region. In 2017, the proportion of induced deliveries was 31.6% in Wallonia[40], 24.6% in Flanders[41], and 28.6% in the Brussels region.[42]

The reimbursement status may also influence the choice of uterotonics. For example, carbetocin (Pabal®) was used much less frequently in the Brussels region than in the other regions in our study. This drug is not reimbursed and is relatively expensive.[43] Some hospitals might prefer to use oxytocin which is reimbursed for preventing uterine atony, instead of Pabal®. The cost may also have an important influence. We observed that the use of misoprostol (Cytotec®) was approximately twice as high in the Brussels region and Flanders compared to that in Wallonia, which might be explained by the low cost of misoprostol (Cytotec®).[44,45]

A study conducted in Sweden reported significant differences in the rate of oxytocin use during labor in different hospitals.[1] According to the authors, these variations might be due to differences in "delivery culture" between hospitals.

Changes in patient demand and expectations may explain some of these variations. We observed a significantly lower rate of oxytocin use in the Brussels region. One hypothesis to explain this result is lower adherence to the recommended routine uterotonics use to prevent PPH in the Brussels region than in Flanders and Wallonia. Several initiatives for low-risk births have recently been established to respond to this demand for less medicalized births in Brussels.[46-48] For example, a new birth center has been established in a large hospital in Brussels to provide a package of care for uncomplicated pregnancies, where the minimisation of medical interventions is encouraged.[48]

Differences in pharmaceutical marketing strategies between regions may explain the observed variations. For example, the increased use of carbetocin, a relatively new uterotonic agent in the Belgian market, might result from pharmaceutical marketing efforts in hospitals that are more sensitive to innovation.

Educational factors might also explain the variation; healthcare workers' education is not equivalent between the different regions in Belgium. Different regional ministries of education and training are responsible for determining the policies of the education system.

Finally, the variations observed reflect the lack of clear national evidence-based guidelines for the use of uterotonics around birth in Belgium. Consequently, the French-speaking portion of Belgium might refer to guidance from France or Switzerland. In contrast, the Flemish-speaking portion might use guidelines from Anglo-Saxon countries or the Netherlands, impacting clinical practices.

Strengths and Limitations

For the first time, this study reports the patterns of uterotonic prescriptions in Belgium. Our sample was representative of the people enrolled in the health security system (98% of the population). We excluded self-employed pregnant women from all three periods because they did not benefit from the same reimbursement scheme throughout the study period. However, we compared the proportions with and without them in the last study period and obtained similar results for uterotonic use. Therefore, we do not believe that it has affected the representativeness of our sample.

Multiparity might influence the use of uterotonics, but because the data were not available before 2003, we were not able to quantify multiparity completely. For the last study period (2015–2018), we checked the number and the proportion of pregnancies with at least one previous pregnancy from the same mother after the year 2003 considering the years between the study periods. We identified 5,163 (50.1%) multiparous pregnancies in the period. We compared the exposure of at least one uterotonic among multiparous pregnancies to the other pregnancies and we found a lower rate of uterotonic use among multiparous pregnancies (90.6 vs 93.1%). Therefore, multiparity may have slightly impacted our results, this factor should be explored in future studies.

The information regarding the exact indications for uterotonics was missing. Our analyses assessed three periods of exposure to distinguish between uterotonics dispensed for labor induction and those dispensed to prevent PPH. However, in the proportion of pregnancies exposed on the day of delivery, we captured prescriptions of uterotonics dispensed for all indications: induction of labor and prevention of PPH. Therefore, any interpretation of indications and conclusions regarding misuse and overuse should be considered with extreme caution.

Finally, there were no validation studies inherent to the measurement of uterotonics with Belgian claims data; however, other studies have shown that claims databases were highly accurate in tracking uterotonics coverage compared to the survey report.[49] We have also presented our results to a team with expertise in gynecology to detect potential clinical contradictions of our results. Additionally, because our data were collected for the primary purpose of billing and reimbursement, controls were performed at different stages to detect inconsistencies in the data, which contributed to their quality.[50]

Conclusion

Most pregnancies in Belgium involve exposure to at least one uterotonic around birth. Between 2003 and 2018, the proportion of pregnancies exposed to at least one uterotonic decreased slightly, suggesting a trend for less medicalized birth experience in Belgium. However, the proportion

of some uterotonics has increased, as with oxytocin and misoprostol use in VB. We also observed significant differences in the proportion of pregnancies exposed to different uterotonics across the three regions of Belgium, emphasizing the need for uniform national guidelines.

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Author Contributions:

LL analyzed the data and drafted the manuscript. XR and GK contributed to data acquisition and interpretation. CDM, PVW, CL, and BD contributed to the interpretation of data and revisions of the manuscript. FKS formulated the objectives and design of the study, supervised the statistical analysis, interpreted the results, and revised the manuscript. All authors were involved in revising the manuscript and approved the final version of the manuscript.

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The authors state that no ethical approval was needed.

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Data that support the findings of this study are available from the InterMutalist Agency (IMA). Restrictions apply to the availability of these data, which were used under license for this study. Data are available at https://metadata.ima-aim.be/fr/app/bdds/Ps with permission from the InterMutalist Agency (IMA).

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Tables:

Table 1. Ages, regions of residence and type of delivery of pregnant mothers in Belgium in the three study periods between 2003 and 2018

	Period 2003–2006 (N = 10,357)	Period 2009–2012 (N = 11,019)	Period 2015–2018 (N = 10,299)
Variables	% (*n*)	% (*n*)	% (*n*)
Maternal age			
< 25 years	16 (1,660)	14.9 (1,636)	11.3 (1,165)
25-29 years	35.5 (3,678)	34.3 (3,779)	32.8 (3,381)
30-34 years	32.7 (3,389)	33.2 (3,660)	35.5 (3,660)
35-39 years	13 (1,343)	14.2 (1,564)	16.2 (1,670)
≥ 40 years	2.8 (287)	3.4 (380)	4.1 (423)
Region of residence			
Flanders	46.6 (4,823)	47.9 (5,277)	49 (5,051)
Wallonia	40.8 (5,225)	39.2 (4,323)	37.8 (3,898)
Brussels region	12.6 (1,309)	12.9 (1,416)	13.1 (1,348)
Delivery type			
Any vaginal birth	81 (8,394)	80.2 (8,833)	78.8 (8,117)
Cesarean section	19 (1,963)	19.8 (2,186)	21.2 (2,182)

Table 2. Prevalence of pregnancies exposed to at least one, two and three different uterotonics agent of the preestablished list dispensed around delivery in Belgium

	Vaginal birth		Cesarean section	
	n/N	% (95%CI)	n/N	% (95%CI)
Proportion of pregnancies exposed to at least one uterotonic agent				
Period 2003-2006	7,798/8,394	92.9 (92.3-93.4)	1,875/1,963	95.5 (94.5-96.4)
Period 2009-2012	8,198/8,833	92.8 (92.2-93.3)	2,066/2,186	94.5 (93.5-95.4)
Period 2015-2018	7,419/8,117	91.4 (90.7-92)	2,045/2,182	93.7 (92.6-94.7)
p-value for trends *		< 0.001		0.011
Proportion of pregnancies exposed to at least two different uterotonic agents**				
Period 2003-2006	3,801/8,394	45.3 (44.2-46.3)	762/1,963	38.8 (36.6-41)
Period 2009-2012	2,804/8,833	31.7(30.8-32.7)	677/2,186	30.1 (29-32.9)
Period 2015-2018	2,084/8,117	25.7 (24.7-26.6)	639/2,182	29.9 (27.4-31.2)
p-value for trends *		< 0.001		<0.001
Proportion of pregnancies exposed to at least three different uterotonic agents**				
Period 2003-2006	845/8,394	10.1 (9.4-10.7)	146/1,963	7.4 (6.3-8.7)
Period 2009-2012	497/8,833	5.6 (5.1-6.1)	151/2,186	6.9 (5.9-8)
Period 2015-2018	271/8,117	3.3 (2.9-3.7)	182/2,182	8.3 (7.2-9.6)
p-value for trends *		<0.001		0.23

* Trend test using logistic regression adjusted on maternal age
** Considered different if ATC code at the 5th level is different
Period of exposure considered: the 7 days preceding childbirth, the day of childbirth and the seven days after childbirth all together.

Table 3. Factors associated to pregnancies exposed to at least one uterotonic agent (2015-2018) N=10,297

	n/N (%)	Adj OR 95 (%CI)	p value
Maternal age			0.01
< 25 years	1,099/1,165 (94.3)	1.39 (1.06-1.1.85)	
25-29 years	3,174/3,381 (92.1)	1 (Ref)	
30-34 years	3,334/3,660 (91.1)	0.88 (0.74-1.04)	
35-39 years	1,524/1,670 (91.3)	0.90 (0.73-1.12)	
≥ 40 years	393/423 (92.9)	1.13 (0.76-1.68)	
Region of residence			<0.001
Flanders	4,619/5,051 (91.4)	1.63 (1.36-1.96)	
Wallonia	3,674/3,898 (94.2)	2.47 (2.01-3.05)	
Brussels region	1,169/1,348 (86.7)	1 (Ref)	
Mode of delivery			<0.001
Any vaginal birth	7,419/8,117 (91.4)	1 (Ref)	
Cesarean section	2,045/2,182 (93.7)	1.42 (1.17-1.72)	
Social Status*			0.87
No preferential rate	7,661/8,333 (91.9)	1 (Ref)	
Preferential rate	1,803/1,966 (91.7)	0.98 (0.74-1.04)	

Adj OR: Adjusted Odd Ratio from logistic regression model
Period of exposure considered: the 7 days preceding childbirth, the day of childbirth and the seven days after childbirth altogether.
*Social status: Pregnant women with a preferential rate is a proxy of low social status

Table 5. Prevalence of pregnancies exposed to at least one prescription of uterotonic dispensed during three different periods of exposure around birth in 2015-2018 (N=10,299)

	7 days before DD		Day of delivery		7 days after DD	
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
oxytocin	987	9.6 (9-10.2)	6,472	62.8 (61.9-63.8)	1,508	14.6 (14-15.3)
dinosprotone	585	5.7 (5.2-6.1)	1,119	10.9 (10.3-11.5)	345	3.3 (3-3.7)
methylergometrine	13	0.1 (0.1-0.2)	194	1.9 (1.6-2.2)	52	0.5 (0.4-0.7)
carboprost	16	0.2 (0.1-0.2)	87	0.8 (0.7-1)	23	0.2 (0.1-0.3)
carbetocin	22	0.2 (0.1-0.3)	733	7.1 (6.6-7.6)	57	0.6 (0.4-0.7)
misoprostol	55	0.5 (0.4-0.7)	317	3.1 (2.7-3.4)	107	1 (0.8-1.2)

DD : Day of Delivery

Table 4. Prevalence of uterotonics prescribed and dispensed around birth between 2003 and 2018

Vaginal only	2003-2006 N=8,394		2009-2012 N=8,833		2015-2018 N=8,117		**p-value for trends ***
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
oxytocin	7,089	84.5 (83.7-85.2)	7,837	88.7(88-89.4)	7,226	89 (88.3-89.7)	<0.001
dinosprotone	1,873	22.3 (21.4-23.2)	1,739	19.7 (18.9-20.5)	1,686	20.8 (19.9-21.7)	0.016
methylergometrine	3,156	37.6 (36.6-38.6)	1,382	15.6 (14.9-16.4)	193	2.4 (2.1-2.7)	<0.001
carboprost	63	0.8 (0.6-0.9)	80	0.9 (0.7-0.11)	91	1.1 (0.9-0.14)	0.011
carbetocin	NA	NA	55	0.6 (0.5-0.8)	82	1 (0.8-1.2)	NA
misoprostol	95	1.1 (0.9-1.4)	359	4 (3.7-4.5)	422	5.2 (4.7-5.7)	<0.001
Cesarean delivery only	2003-2006 N=1,963		2009-2012 N=2,186		2015-2018 N=2,182		**p-value for trends ***
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
oxytocin	1,824	92.9 (91.7-94)	1,835	83.9 (82.3-85.5)	1,536	70.4 (68.4-72.3)	<0.001
dinosprotone	29	15.2 (13.7-16.9)	311	14.2 (12.8-15.8)	316	14.5 (13-16)	0.75
methylergometrine	540	27.5 (25.5-29.5)	279	12.8 (11.4-14.2)	65	3 (2.3-3.8)	<0.001
carboprost	16	0.8 (0.5-1.3)	31	1.4 (0.9-2)	33	1.5 (1-2.1)	0.047
carbetocin	NA	NA	339	15.5 (14-17.1)	729	33.4 (31.4-35.4)	NA
misoprostol	18	0.9 (0.5-1.4)	46	2.1 (1.5-2.8)	56	2.6 (1.9-3.3)	<0.001

* Trend test using logistic regression analyses adjusted on maternal age at birth.

NA = Not Applicable: Carbetocin was not yet commercialized in Belgium in the period 2003-2006.

Period of exposure considered: the 7 days preceding childbirth, the day of childbirth and the seven days after childbirth all together.

Table 6. Geographical variations in the proportion of pregnancies exposed to at least one uterotonic agent at the end of pregnancy in 2015-2018

Vaginal only	Flanders N=3,987		Wallonia N=3,066		Brussels region N=1,063		p-value *
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
Oxytocin	3,532	88.6 (87.6-89.5)	2,827	92.2 (91.2-93.1)	866	81.5 (79-83.8)	< 0.001
Dinoprostone	871	21.8 (20.6-23.2)	650	21.2 (19.8-22.7)	165	15.5 (13.4-17.8)	< 0.001
Misoprostol-Cytotec	252	6.3 (5.6-7.1)	115	3.8 (3.1-4.5)	54	5.1 (3.8-6.6)	< 0.001
Methylergometrine	94	2.4 (1.9-2.9)	74	2.4 (1.9-3)	25	2.4 (1.5-3.4)	0.97
Carboprost	33	0.8 (0.6-1.2)	45	1.5 (1.1-1.9)	13	1.2 (0.6-2.1)	0.045
Carbetocin	51	1.3 (0.9-1.7)	30	1 (0.7-1.4)	<5	<0.1 (---)	0.021
Cesarean delivery only	Flanders N=1,064		Wallonia N=832		Brussels region N=285		p-value *
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
Oxytocin	731	68.7 (65.8-71.5)	594	71.4 (68.2-74.4)	210	73.7 (68.2-78.7)	0.15
Dinoprostone	145	13.6 (11.6-15.8)	125	15 (12.7-17.6)	46	16.1 (12.1-20.1)	0.47
Misoprostol-Cytotec	31	2.9 (2-4.1)	17	2 (1.2-3.2)	8	2.8 (1.2-5.5)	0.5
Methylergometrine	47	4.4 (3.3-5.8)	12	1.4 (0.7-2.5)	6	2.1 (0.8-4.5)	<0.001
Carboprost	9	0.8 (0.4-1.6)	20	2.4 (1.5-3.7)	<5	<1.5 (---)	0.035
Carbetocin	353	33.2 (30.3-36.1)	322	38.7 (35.4-42.1)	54	18.9 (14.6-24)	<0.001

* P value from logistic regression adjusted on maternal age
Period of exposure considered: the 7 days preceding childbirth, the day of childbirth and the seven days after childbirth all together.

Figure:

Figure 1. Flowchart of the study