



HAL
open science

Risk factors for very preterm delivery out of a level III maternity unit: The EPIPAGE-2 cohort study

Thomas Desplanches, Andrei Morgan, Peter Jones, Caroline Diguisto, Jennifer Zeitlin, Laetitia Martin-marchand, Valérie Benhammou, Bénédicte Lecomte, Jean-christophe Rozé, Patrick Truffert, et al.

► To cite this version:

Thomas Desplanches, Andrei Morgan, Peter Jones, Caroline Diguisto, Jennifer Zeitlin, et al.. Risk factors for very preterm delivery out of a level III maternity unit: The EPIPAGE-2 cohort study. Paediatric and Perinatal Epidemiology, 2021, 35 (6), pp.694-705. 10.1111/ppe.12770 . hal-03472188

HAL Id: hal-03472188

<https://uca.hal.science/hal-03472188>

Submitted on 5 Dec 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Title page: Risk factors for very preterm delivery out of a level III maternity unit: The EPIPAGE-2 cohort study.

A short running title: Risk factors and avoidability of outborn birth.

Full names of the authors: Thomas Desplanches^{1,2}, Andrei S Morgan^{1,3,4}, Peter Jones^{5,6}, Caroline Diguisto^{1,7}, Jennifer Zeitlin¹, Laetitia Martin-Marchand¹, Valérie Benhammou¹, Bénédicte Lecomte⁸, Jean-Christophe Rozé⁹, Patrick Truffert¹⁰, Pierre-Yves Ancel^{1,11}, Paul Sagot², Adrien Roussot¹², Jeanne Fresson^{1,13}, Béatrice Blondel¹.

Author's institutional affiliations:

¹Obstetrical, Perinatal, and Pediatric Epidemiology Team, Center of Research in Epidemiology and Statistics (U1153), Université de Paris, INSERM, Paris, France.

²CHRU Dijon, Department of gynecology, obstetrics, fetal medicine and infertility, Dijon, France.

³ Department of Neonatology, Elizabeth Garrett Anderson Institute for Women's Health, UCL, London.

⁴ Embrace Yorkshire and Humber Infant and Paediatric Transport Service, Sheffield Children's Hospital NHS Foundation Trust, Sheffield, UK

⁵ SAMU de Paris, AP-HP, Hôpital Necker Enfants Malades, 149 Rue de Sèvres Paris 75015

⁶ Réanimation Pédiatrique AP-HP, Hôpital Robert Debré, 48 Bd Sérurier Paris 75019.

⁷ Department of Obstetrics and Gynecology, University Hospital of Tours, Tours University, France

⁸ Estaing University Hospital, Clermont-Ferrand, France.

⁹ Pediatric Intensive Care Unit, Mothers' and Children's Hospital, Nantes Teaching Hospital, Nantes, France.

¹⁰ Neonatal Intensive Care Unit, Jeanne de Flandre Hospital, CHRU Lille, Lille, France.

¹¹ Clinical Research Unit, Center for Clinical Investigation P1419, CHU Cochin Broca Hôtel-Dieu, Paris, France.

¹² Biostatistics and Bioinformatics (DIM), University Hospital, Dijon, France; Bourgogne Franche-Comté University, Dijon, France

¹³ Department of Medical Information, University Hospital (CHRU) Nancy, France

Address correspondence to: Thomas Desplanches – Obstetrical, Perinatal, and Pediatric Epidemiology Team, Center of Research in Epidemiology and Statistics (U1153), Université de Paris, INSERM, Paris, France. thomas.desplanches@inserm.fr

Authorship

T Desplanches was involved in study design, analysis and interpretation of the results and drafted the initial manuscript and revised the manuscript; B Blondel, J Fresson and J Zeitlin discussed the design of the study. B Blondel, J Fresson, L Marchand-Martin, C Diguisto, AS Morgan and J Zeitlin were involved in study design, analysis, and interpretation of data, and reviewed the manuscript. V Benhammou, B Lecomte, JC Rozé, P Truffert, P Jones, P Sagot, A Roussot, and PY Ancel critically reviewed the manuscript for important intellectual content. PY Ancel has overall scientific responsibility for the cohort. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Social media quote.

Tweetable 266/280 characters.

Despite the widespread use of antenatal transfer in France, 16% of very preterm deliveries did not occur in a level III unit. Of these, 42% were probably (17%) or possibly (25%) avoidable; improving access to these specialized units needs better referral strategies.

Synopsis (124/125 Words).

Study question. What are the principal social and clinical risk factors associated with very preterm delivery outside of a level III unit and are these outborn deliveries avoidable?

What's already known? Obstetric complications, lower social status and residing far from a level III unit have been identified as risk factors in previous studies.

What this study adds? In France, despite a high use of antenatal transfer (50% of inborn deliveries), 16% of very preterm deliveries (24-30⁺⁶ weeks) did not occur in a level III unit. Risk factors were inadequate antenatal care, placental abruption, extremely preterm delivery and increased distance to level III. Among outborn deliveries, 17% were probably avoidable and 25% possibly avoidable; consequently, achieving full access to tertiary care requires improved referral strategies.

Abstract. (298 /300 words).

Background: Regionalisation programmes aim to ensure that very preterm infants are born in level III maternity units (inborn) through referral or antenatal transfer before delivery. Despite widespread knowledge about better survival without disability for inborn babies, 10 to 30% of women deliver outside these units (outborn).

Objective: To investigate principal risk factors associated with outborn deliveries and to estimate the proportion that were probably or possibly avoidable.

Methods: We used a national French population-based cohort including 2,205 women who delivered between 24 and 30⁺⁶ weeks. We examined risk factors for outborn delivery related to medical complications, antenatal care, sociodemographic characteristics and living far from a level III unit using multivariable binomial regression. Avoidable outborn deliveries were defined according to pregnancy risk (obstetric history, antenatal hospitalisation) and time available for transfer (length of stay in hospital immediately before delivery).

Results: 49.8% of women delivered in level III unit after antenatal transfer and 34.1% without transfer (total 83.9%). Risk factors for outborn delivery were: gestational age <26 weeks (RR 1.4, 95% CI 1.1, 1.7), inadequate antenatal care (RR 1.4, 95% CI 1.1, 1.8), placental abruption (RR 1.7, 95% CI 1.3, 2.2) and increased distance to the closest level III unit (RR 2.8, 95% CI 2.0, 3.9) in the 4th versus 1st distance quartile). Among outborn deliveries, 16.7% were probably avoidable and 25.6% possibly avoidable, which could increase the proportion of inborn deliveries between 2 and 9%. Avoidable outborn deliveries were mainly associated with gestational age, intrauterine growth restriction, preterm premature rupture of membranes, and haemorrhage, but not distance.

Conclusions: Our study identified some modifiable risk factors for outborn delivery; however, only some avoidable situations may be prevented when regionalised care relies heavily on antenatal transfer. Earlier referral of high-risk women will be needed to achieve full access to tertiary care.

Key words: place of delivery; very preterm birth; obstetric care; geographical access; perinatal epidemiology, antenatal transfer.

Word count: 3452/3500

Main text

Background

Many studies have shown that the delivery of very low birth weight (VLBW) or very preterm (VPT) infants in maternity units with an on-site neonatal intensive care unit, generally called level III units, is associated with lower mortality and higher survival without disability.¹⁻⁴ Most high-income countries have implemented regionalisation policies to transfer pregnant women at high risk of VPT delivery to a hospital with the appropriate level of neonatal care.^{1, 5} However, studies show that up to a quarter of these high risk births occur outside of a level III maternity unit (termed outborn deliveries).^{2, 6-11} Some of these cases result from emergency situations, for instance, imminent delivery or maternal haemorrhage where transfer is not safe. However, it is likely that a number of outborn deliveries could be avoided by earlier referral or transfer of women with risk factors or symptoms to level III units.^{12, 13} Long distance to the closest unit has also been shown to raise the probability of outborn birth.¹⁴

In order to reduce outborn deliveries, knowledge is needed about the social and medical characteristics associated with delivery out of level III. Although previous studies have shown that the success of regionalisation varies widely^{3, 8, 10}, few studies on associated factors have been carried out.^{6, 7, 14, 15} Considering the varied approaches to regionalisation worldwide, additional studies are needed to better understand how to obtain a high level of regionalisation. In France, where perinatal regionalisation was introduced in 1998,¹⁶ previous analyses have only been carried out in two regions.^{14, 15}

Our objectives were i) to investigate the association between risk factors (medical and sociodemographic factors, and distance to the closest level III unit) and outborn delivery, and ii)

to estimate the proportion of outborn deliveries that may have been avoided based on an assessment of pregnancy risk and the time available for transfer before delivery. This study was based on a large national cohort of women who gave birth to very preterm infants in France.

Methods

Population

The prospective population-based EPIPAGE 2 cohort (Etude Epidémiologique sur les Petits Âges Gestationnels) included all births occurring between 22 and 31 completed weeks of gestation (WG) in 25 out of the 26 French regions in 2011. Recruitment lasted 8 months for women who gave birth at 22 to 26 WG and 6 months for births at 27 to 31 WG. Details about the design and methods have been described previously.¹⁷ For this study, the population was restricted to mothers who resided in metropolitan France, with at least one live foetus between 24 and 30 completed WG at the onset of labour, or when a caesarean section was decided. We excluded women who delivered after 30⁺⁶ WG because the recommendations allow for the management of these births in lower-level hospitals in some regions. We also excluded pregnancies with a lethal congenital malformation and terminations of pregnancy. No deliveries occurred during antenatal transfer.

Outcome measures

The outcome was delivery outside of a level III maternity unit. Levels of care are based on a three-tiered system defined by a national regulation¹⁶ which includes level III units (defined as the highest level of care for preterm births (inborn deliveries)), level II units, which are equipped to manage preterm births from 31-32 to 36 completed weeks of gestation, and units without a

neonatal unit (level I maternity units). At a regional level, all maternity units are part of a perinatal network which defines, in particular, the criteria for transfer.

Four groups were defined: women who had initially planned to deliver in level III maternity units, women who delivered in level maternity III units after referral (defined as outpatients sent to a level III unit for follow-up/delivery for medical reasons), women who were transferred to level III maternity units before delivery, and women who delivered outside level III maternity units (outborn deliveries).

We also created a classification assessing the avoidability of outborn delivery (unavoidable, possibly avoidable, probably avoidable) based on three criteria: the length of stay in hospital immediately before delivery, antenatal hospitalization after 22 WG, and history of severe perinatal complications defined as previous stillbirth (≥ 22 WG) or extreme preterm delivery (between 22 and 28 WG). Outborn delivery was considered to be unavoidable if the length of stay was less than 24 hours, there was no antenatal hospitalization, and there was no history of severe perinatal complications. It was considered possibly avoidable if the length of stay was less than 24 hours and there was either a history of severe perinatal complications or antenatal hospitalization, or if the length of stay was between 24 and 48 hours and there was no antenatal hospitalization, and no history of severe perinatal complications. Finally, deliveries were considered probably avoidable if the woman was hospitalised before delivery for more than 48 hours, or if the length of stay was between 24 and 48 hours and there was either antenatal hospitalization or a history of severe perinatal complications (Figure 1).

Variables

Co-variables included maternal demographic, social and medical/clinical characteristics hypothesized to affect the probability of delivering in a level III unit based on previous research: maternal age, maternal country of birth (France or another country), parental socioeconomic status (the highest occupational status of the mother and the father, or mother only if a single parent), pre-existing maternal comorbidity (type 1 diabetes or high blood pressure), adverse obstetric history (previous stillbirth or preterm birth), pregnancy characteristics: infertility treatment, parity, multiple pregnancy, complications of pregnancy (preterm labour, preterm premature rupture of membranes (PPROM), hypertensive disorders of pregnancy (HDP),¹⁸ placental abruption, pregnancy-related infection (i.e. chorioamniotitis) and, antenatal diagnosis of intrauterine growth restriction (IUGR)), gestational age at delivery (in completed weeks of gestation) and inadequate antenatal care defined by less than a monthly visit as recommended by French national guidelines.¹⁹

We also included measures of distance and travel time from each woman's residence to the closest level III maternity unit based on postal codes using Chronomap[®] software from Geographical Information System MapInfo v11.0. The road network was the network provided by IGN500[®] from the French national geographic institute (*Institut national de l'information géographique et forestière*). We then grouped distance and time measures by quartile.

Statistical analysis

We first described the place of delivery and antenatal and postnatal transfers in our study population.

To identify the risk factors for delivery out of a level III maternity unit, women who gave birth to VPT infants in a non-level III unit were compared with all women who delivered in level III maternity units.

To investigate risk factors specifically linked with failure of antenatal transfer, a second set of analyses compared the characteristics of women who delivered in a level III maternity unit after antenatal transfer with women who had an outborn delivery.

Finally, we assessed the proportion of women who could have given birth in level III units according to our criteria of avoidability. Given the low number of women in the possibly and probably avoidable groups, they were combined to compare the major risk factors of women for whom not delivering in level III was possibly or probably avoidable with those for whom not delivering in level III was unavoidable.

All percentages and tests were weighted to account for the differing durations of recruitment period by gestational age group. In multivariable analyses, all covariables were considered to be potential risk factors and included in the models. Risk ratios were estimated using log-binomial regression models. Generalized estimating equation (GEE) regression analysis was used in order to take into account clustering of women within regions.²⁰

All analyses were carried out with SAS v9.4 software.

Missing data

Residential postal codes were missing in 7.8% of cases hence these women were excluded from analyses. Most other variables included in the models had fewer than 5% of missing data. However, the percentage of missing data was between 5% and 10% for maternal country of birth, parental socioeconomic status and antenatal care. Analyses of risk factors for outborn deliveries

were done using multiple imputations (chained equations with a logistic regression imputation model for missing binary data and a multinomial imputation model for missing categorical data).²¹ Imputation model variables included maternal characteristics: maternal age, parity, parental socioeconomic status, country of birth, infertility treatment, maternal comorbidity, adverse obstetric history, multiple pregnancy, inadequate antenatal care, gestational age, and complications of pregnancy. We generated 50 independent imputed datasets. Estimates were pooled according to Rubin's rule.²¹ Further details are available in eTable 1.

Sensitivity analyses.

We carried out two analyses to assess the sensitivity of our results to our choice of analytic strategy: (1) we ran our models using travel time instead of travel distance and (2) we did the analyses on complete cases.²²

Ethics approval

This study was approved by the National Data Protection Authority (CNIL no.911009) and by the appropriate ethics committees (Consultative Committee on the Treatment of Data on Personal Health for Research Purposes - reference no. 10.626, Committee for the Protection of People Participating in Biomedical Research - reference CPP SC-2873).

Results

Delivery outside of a level III unit

Of the 2,205 women who were included in our analysis, 16.1% gave birth outside a level III maternity unit, 25.0% delivered in a level III unit after initial booking, 9.1% delivered in a level III after referral during pregnancy and 49.8% delivered in a level III after antenatal transfer (Figure 2).

Of the 413 VPT outborn infants (out of 2,606 total infants), 295 (71.4%) were transferred to a neonatal intensive care unit (NICU), 85 (20.6%) died (stillbirth or death in delivery room) and 33 (8.0%) were not transferred to a NICU.

Characteristics of outborn deliveries versus inborn deliveries according to referral or antenatal transfer status

Table 1 shows that women with outborn delivery had fewer comorbidities, fewer foetuses with IUGR, and lived farther from level III maternity units than women who delivered in level III unit after referral. Preterm labour and placental abruption occurred more frequently in outborn deliveries than inborn deliveries after an antenatal transfer. There was no difference in distance to the level III units between outborn deliveries and inborn deliveries after an antenatal transfer in contrast with observed differences between outborn deliveries and those in level III after initial booking or referral.

Risk factors for not delivering in a level III maternity unit

In the multivariable analysis shown in Table 2, outborn deliveries were associated with very low gestational age (24-25 WG) (RR 1.37, 95% confidence interval (CI) 1.13, 1.66), inadequate antenatal care (RR 1.39, 95% CI 1.10, 1.81) and placental abruption (RR 1.66, 95% CI 1.27, 2.17). Multiple pregnancy, having a comorbidity or adverse obstetric history were not associated with a lower risk of outborn delivery. Increased distance was a risk factor for not delivering in level III units: compared to the first quartile (1-6 km), the RR for living in the 2nd quartile (6 to 17 km) was 1.80 (95% CI 1.35, 2.41) rising to 2.79 (95% CI 2.00, 3.92) for the 4th quartile (distance of 48 km or more).

Risk factors associated with outborn delivery were the same in the analysis only considering women who were receiving care outside of level III units before delivery and therefore candidates for antenatal transfer (Table 3). The one exception was distance; the probability of outborn birth was lower in the 1st quartile, but risks were similar across the remaining quartiles (Table 3).

Results were similar in the sensitivity analyses using travel time from the woman's residence to her closest level III unit instead of the distance (not shown) as well as in complete case analyses (eTable 2 and 3).

Avoidability

The assessment of avoidability focused on 317 outborn deliveries (missing data n=23, exclusion of home births n=26). According to our criteria, 16.7% of women who delivered outside level III maternity units were classified as "probably avoidable", 25.6% as "possibly avoidable" and 57.7% as "unavoidable". Accordingly, the proportion of inborn deliveries could increase between 2% (probably avoidable) and 9% (probably and possibly avoidable).

Avoidable outborn deliveries were associated with gestational age, with a higher risk at 24-25 WG (RR 1.47, 95% CI 1.14, 1.90) and at 28-30⁺⁶ WG (RR 1.29, 95% CI 1.05, 1.57) and with three complications: IUGR, PPROM and haemorrhage, but were not associated with distance to the nearest level III unit (Table 4).

Comment

Principal findings

In our population-based cohort, most VPT deliveries (83.9%) occurred in level III maternity units, with a high proportion (49.8%) of women transferred just before delivery (antenatal transfer) and a smaller proportion (only 9.1%) of women being referred during pregnancy. Risk factors for not delivering in a level III maternity unit were inadequate antenatal care, placental abruption, extremely preterm delivery and a long distance to the closest level III. Finally, we estimated that 16.7% of outborn deliveries were probably avoidable and 25.6% possibly avoidable, mainly for extremely preterm deliveries or deliveries close to 30 weeks or in cases of IUGR, PPROM, and haemorrhage.

Strengths and limitations of this study

The EPIPAGE-2 study is a large national population-based prospective cohort. This database includes numerous socio-demographic and medical data, allowing us to study key drivers of the regionalisation of perinatal care. Consequently, we were able to analyse the circumstances related to preterm delivery outside of a level III unit and to evaluate to what extent these outborn deliveries could have been avoided.

The main limitation is that the number of outborn deliveries was low, and did not allow for stratified analyses by sub-groups. For instance, analysing risk factors by week of gestational age

would have been particularly relevant at 24-25 WG and at 30 WG since transfer policies at these gestational ages might vary by region. The number of home births was also very low, and they were therefore not analysed. In addition, our data were collected in 2011. The situation may have changed over time, but routine hospital discharge statistics show that the national inborn rate has remained stable in infants born between 24 and 30 completed WG (83.2% in 2013, 84.6% in 2018).²³

Interpretation

To obtain a high level of regionalisation, each country organises their obstetrics services differently, for instance with a high concentration of total deliveries in specialised units or an elevated proportion of referrals of high-risk women to specialised units before delivery.⁸ In France, maternity care is provided by small and large units spread throughout the country, and only 23% of all deliveries occur in level III maternity units.²⁴ The high proportion of inborn deliveries in our study is thus obtained through a high rate of antenatal transfer (49.8%) and also by referral during pregnancy, although this represented a much smaller proportion of women (9.1%).

The high inborn and antenatal transfer rates reveal effective coordination between health professionals within perinatal networks, but a substantial number of VPT infants are still not being born in optimal conditions in France. Some countries have achieved higher proportions of inborn deliveries; for instance, in Finland this proportion increased from 84% in 2006 to 95% in 2017 in new-borns under 32 WG and was followed by an improvement in their survival rates.¹⁰ In other countries,^{3, 25} regionalisation policies have not been sufficiently implemented despite recommendations. In the UK for instance, consequences included higher numbers of early

postnatal transfers and lower rates of survival without severe brain injury in outborn infants compared with inborn infants.¹⁰

Our analysis identified some key factors that led to failure to deliver in a level III unit: inadequate antenatal care, some complications of pregnancy, low gestational age and distance to the closest level III unit.

The role of inadequate antenatal care was highlighted in previous studies.^{6, 7} It could result in both the lack of referral during pregnancy and of antenatal transfer, perhaps due to delays to visit a physician, or more emergency presentations at non-level III maternity units prior to delivery. As expected, we found that placental abruption (7% of deliveries) increased the risk of outborn delivery. Other pregnancy complications, including antenatal diagnosis of IUGR, HDP, pregnancy-related infection, and PPRM, were associated with lower risks of outborn delivery. These are recognised risk factors for VPT delivery and are not usually associated with the need for immediate delivery; therefore, better management of most of these complications could improve inborn rates, as shown by the analysis of the risk factors for outborn deliveries considered to be probably or possibly avoidable.

The probability of outborn deliveries was higher for the lowest gestational ages, which most likely results from a reluctance to transfer at extreme gestational ages in the guidelines of some perinatal networks. We found that the proportion of avoidable outborn deliveries was higher at these low gestational ages, and thus the prognosis of these infants could have been improved, as shown in other countries.²⁶ In order to achieve optimal regionalisation, the gestational age threshold of antenatal transfer should be lowered to facilitate active management of extremely preterm births.

As in previous studies, we observed that long distance had an impact on the probability of outborn birth.^{6, 7, 14} However, we add to this body of research by distinguishing between women who originally planned to give birth in a level III unit and those who were referred or transferred. We found that the risk of outborn delivery increased with distance when we compared outborn deliveries with all deliveries in level III units. However, it did not increase with the longest distances (3rd and 4th quartile) when the analysis was limited to women eligible for antenatal transfer.

This suggests that the strongest impact of distance on regionalisation relates to initial booking or referral decisions (Table 1). For women who need a transfer, caregivers have to take distance into account to the level III in their decision to transfer or not. In addition, a long drive from the woman's home to the level III unit is a relatively small part of the total time needed for the transfer, and thus a small part of the success of transfer policies.²⁷

Socio-economic status has also been shown to influence the probability of not delivering in level III.^{6, 12} In our multivariable analysis, women with a lower socio-economic status were not more likely to deliver outside a level III unit. This may be related to the characteristics of level III maternity units in France which are all public facilities and that are often located in the largest metropolitan areas where low-income or disadvantaged populations are concentrated.

Although multiple pregnancies are at much higher risk of preterm birth and thus have a more intensive follow-up, as recommended,²⁸ the risk of outborn deliveries was not lower than for singleton pregnancies. Likewise, women with comorbidities or adverse obstetric history were not at a lower risk of outborn deliveries, which suggests that referrals of high-risk women can be improved.

Our investigation of avoidable outborn deliveries raises questions about the organization of care, and in particular the strategy for antenatal transfers between maternity units. Very few studies have described the avoidability of outborn deliveries using a large cohort of preterm births,²⁹ and there is no definition available in the literature. We chose to select well-known indicators based on history of severe perinatal complications and antenatal hospitalization.³⁰ In addition, in order to ensure the feasibility of a transfer, we took into account the length of time between admission to hospital and delivery because it is easier to make a decision to transfer when the woman is already hospitalized and childbirth is not imminent.

Our results suggest that transfer decisions could be improved for some women. The importance of these results is further highlighted by a recent study conducted by Shah et al showing that improved antenatal transfer may be associated with lower mortality.¹² We found that optimizing transfers could lead to a maximum increase of 9% in the inborn delivery rate, though an increase of 2% is more likely. Therefore, an improved referral strategy is needed to maximize access to tertiary care.

One of the main concerns relative to regionalisation is that an increase of antenatal transfers requires the allocation of additional resources. However, a recent study showed that both the costs and the need for antenatal maternal beds in level III units were low when the strategy of regionalisation was implemented for VPT deliveries.³¹

Finally, given the number of unavoidable outborn deliveries, specific training should be provided routinely to staff in level I and II maternity units for the management of VPT new-borns.

Conclusions

Despite a long-standing policy of regionalisation of perinatal care for very preterm births in France, our study found that barriers remain. Regionalisation relies on antenatal transfer, which is a complex procedure that is often carried out in an emergency context. Although we identified modifiable risk factors and avoidable situations which could contribute to reductions in the outborn rate, our study suggests that achieving full access to tertiary care for very preterm births will also require better referral strategies during pregnancy to level III units for women at high risk of preterm birth.

References

1. Lasswell SM, Barfield WD, Rochat RW, Blackmon L. Perinatal regionalization for very low-birth-weight and very preterm infants: a meta-analysis. *JAMA*. 2010; 304:992-1000.
2. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. *Arch Dis Child Fetal Neonatal Ed*. 2014; 99:F181-8.
3. Gale C, Santhakumaran S, Nagarajan S, Statnikov Y, Modi N, Neonatal Data Analysis U, et al. Impact of managed clinical networks on NHS specialist neonatal services in England: population based study. *BMJ*. 2012; 344:e2105.
4. Amer R, Moddemann D, Seshia M, Alvaro R, Synnes A, Lee KS, et al. Neurodevelopmental Outcomes of Infants Born at <29 Weeks of Gestation Admitted to Canadian Neonatal Intensive Care Units Based on Location of Birth. *J Pediatr*. 2018; 196:31-7 e1.
5. Rashidian A, Omidvari AH, Vali Y, Mortaz S, Yousefi-Nooraie R, Jafari M, et al. The effectiveness of regionalization of perinatal care services--a systematic review. *Public Health*. 2014; 128:872-85.
6. Bronstein JM, Capilouto E, Carlo WA, Haywood JL, Goldenberg RL. Access to neonatal intensive care for low-birthweight infants: the role of maternal characteristics. *Am J Public Health*. 1995; 85:357-61.
7. Samuelson JL, Buehler JW, Norris D, Sadek R. Maternal characteristics associated with place of delivery and neonatal mortality rates among very-low-birthweight infants, Georgia. *Paediatr Perinat Epidemiol*. 2002; 16:305-13.

8. Blondel B, Papiernik E, Delmas D, Kunzel W, Weber T, Maier RF, et al. Organisation of obstetric services for very preterm births in Europe: results from the MOSAIC project. *BJOG*. 2009; 116:1364-72.
9. Hossain S, Shah PS, Ye XY, Darlow BA, Lee SK, Lui K, et al. Outborns or Inborns: Where Are the Differences? A Comparison Study of Very Preterm Neonatal Intensive Care Unit Infants Cared for in Australia and New Zealand and in Canada. *Neonatology*. 2016; 109:76-84.
10. Helenius K, Longford N, Lehtonen L, Modi N, Gale C, Neonatal Data Analysis U, et al. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. *BMJ*. 2019; 367:l5678.
11. Neto MT. Perinatal care in Portugal: effects of 15 years of a regionalized system. *Acta Paediatr*. 2006; 95:1349-52.
12. Shah KP, deRegnier RO, Grobman WA, Bennett AC. Neonatal Mortality After Interhospital Transfer of Pregnant Women for Imminent Very Preterm Birth in Illinois. *JAMA Pediatr*. 2020.
13. Whitham M, Dudley DJ. Delivering Neonates at High Risk in the Right Place: Back to the Future Again. *JAMA Pediatr*. 2020.
14. Pilkington H, Blondel B, Papiernik E, Cuttini M, Charreire H, Maier RF, et al. Distribution of maternity units and spatial access to specialised care for women delivering before 32 weeks of gestation in Europe. *Health Place*. 2010; 16:531-8.
15. Zeitlin J, Gwanfogbe CD, Delmas D, Pilkington H, Jarreau PH, Chabernaude JL, et al. Risk factors for not delivering in a level III unit before 32 weeks of gestation: results from a population-

- based study in Paris and surrounding districts in 2003. *Paediatr Perinat Epidemiol.* 2008; 22:126-35.
16. Ministère de l'emploi et de la solidarité. Décret n°98-899 et n°98-900 du 9 octobre 1998. *Journal officiel de la république française.* 1998 ;15343.
17. Ancel PY, Goffinet F, Group EW. EPIPAGE 2: a preterm birth cohort in France in 2011. *BMC Pediatr.* 2014; 14:97.
18. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P, Canadian Hypertensive Disorders of Pregnancy Working G, et al. The hypertensive disorders of pregnancy (29.3). *Best Pract Res Clin Obstet Gynaecol.* 2015; 29:643-57.
19. Haute autorité de santé. Suivi et orientation des femmes enceintes en fonction des situations à risque identifiées. 2016. Available at https://www.has-sante.fr/upload/docs/application/pdf/suivi_orientation_femmes_enceintes_synthese.pdf (accessed June 2020).
20. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology.* 2010; 21:467-74.
21. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med.* 1991; 10:585-98.
22. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011; 30:377-99.
23. Agence technique de l'information sur l'hospitalisation Available at <https://www.scansante.fr/applications/indicateurs-de-sante-perinatale> (accessed June 2020).

24. Blondel B, Lelong N, Kermarrec M, Goffinet F, National Coordination Group of the National Perinatal S. Trends in perinatal health in France from 1995 to 2010. Results from the French National Perinatal Surveys. *J Gynecol Obstet Biol Reprod (Paris)*. 2012; 41:e1-e15.
25. Haberland CA, Phibbs CS, Baker LC. Effect of opening midlevel neonatal intensive care units on the location of low birth weight births in California. *Pediatrics*. 2006; 118:e1667-79.
26. Ancel PY, Goffinet F, Group E-W, Kuhn P, Langer B, Matis J, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr*. 2015; 169:230-8.
27. Gale C, Hay A, Philipp C, Khan R, Santhakumaran S, Ratnavel N. In-utero transfer is too difficult: results from a prospective study. *Early Hum Dev*. 2012; 88:147-50.
28. Vayssiere C, Benoist G, Blondel B, Deruelle P, Favre R, Gallot D, et al. Twin pregnancies: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol*. 2011; 156:12-7.
29. Lecoeur C, Thibon P, Prime L, Mercier PY, Balouet P, Durin L, et al. Frequency, causes and avoidability of outborn births in a French regional perinatal network. *Eur J Obstet Gynecol Reprod Biol*. 2014; 179:22-6.
30. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008; 371:75-84.
31. Helenius K, Helle E, Lehtonen L. Amount of Antenatal Care Days in a Context of Effective Regionalization of Very Preterm Deliveries. *J Pediatr*. 2016; 169:81-6.

Acknowledgments: The authors would like to thank Suzanne Rankin for editing and proofreading the manuscript. Special thanks go to Monique Kaminski for her very careful reviewing of the paper.

We are grateful for the participation of all families of preterm infants in the EPIPAGE-2 cohort study and for the cooperation of all maternity and neonatal units in France. We thank parents' associations (SOS Prema, Collectif Interassociatif Autour de la NaissancE (CIANE), Jumeaux et Plus, Soins Palliatifs et Accompagnement en MAternité (SPAMA)) for their overwhelming support and their involvement in the dissemination of the results. We thank the EPIPAGE-2 study group for its substantial contribution to conception, design, and data acquisition.

Funding

The survey was supported by the French Institute of Public Health Research/ Institute of Public Health and its partners the French Health Ministry, the National Institute of Health and Medical Research, the National Cancer Institute and the National Solidarity Fund for Autonomy; grant ANR-11-EQPX-0038 from the National Research Agency through the French Equipex Program of Investments in the Future; the PremUp Foundation and Fondation pour la Recherche Médicale. TD had a grant from the Association nationale pour la formation permanente du personnel hospitalier (ANFH).

Figures

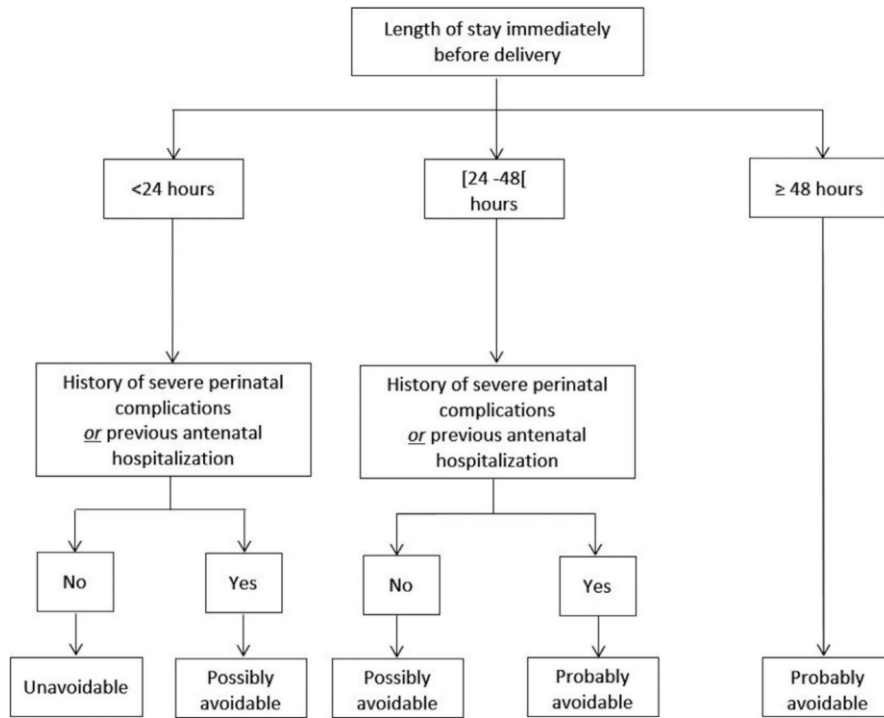


Figure 1: Definition of avoidability groups.

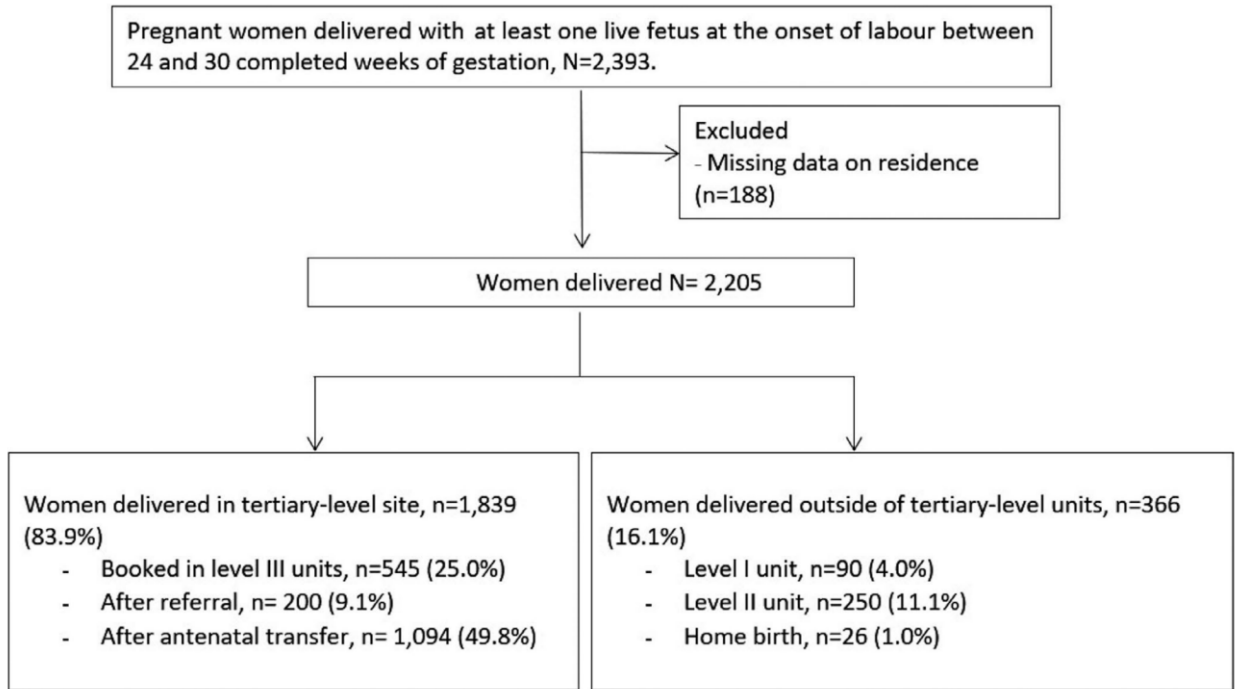


Figure 2: flow chart.

Table 1: Maternal, pregnancy and accessibility characteristics (%), by place of delivery and transfer or referral status.

Characteristics	Delivery in level III units as planned	Delivery in level III units after a referral	Delivery in level III units after an antenatal transfer	Delivery outside level III units
N= 2,205	N= 545	N=200	N= 1,094	N=366
Maternal, n (%)				
Maternal age. (years)				
< 25	100 (18.3)	32 (16.1)	204 (18.7)	99 (26.6)
25-34	326 (59.5)	112 (56.8)	645 (59.0)	208 (57.2)
≥35	119 (22.1)	55 (27.1)	244 (22.4)	59 (16.1)
Birth out of France	145 (29.3)	36 (19.9)	222 (22.3)	57 (17.4)
Socioeconomic status				
Professional/Intermediate	203 (40.8)	84 (45.1)	418 (41.2)	106 (33.2)
Employee/worker	264 (53.6)	101 (53.2)	578 (56.4)	198 (61.8)
Not employed	29 (5.6)	3 (1.7)	24 (2.4)	18 (5.0)
Maternal comorbidity	30 (5.6)	19 (9.7)	49 (4.5)	13 (3.8)
Adverse obstetric history	44 (8.0)	14 (7.0)	63 (5.6)	26 (7.2)
Pregnancy, n (%)				
Infertility treatment	74 (14.1)	25 (12.5)	161 (14.8)	31 (8.6)
Multiple pregnancy	116 (21.3)	42 (21.2)	218 (19.8)	57 (15.6)
Nulliparous women	273 (50.4)	100 (50.3)	621 (57.2)	190 (51.9)
Inadequate antenatal care	54 (10.3)	6 (3.1)	46 (4.5)	44 (12.5)
Preterm labour	223 (35.3)	46 (22.1)	403 (36.1)	188 (54.3)
PPROM	198 (36.1)	57 (27.9)	446 (39.8)	61 (12.0)
Haemorrhage	135 (25.2)	32 (16.3)	216 (19.6)	73 (21.4)
Placental abruption	39 (7.4)	12 (6.1)	57 (5.2)	40 (16.4)
HDP	105 (19.9)	68 (34.7)	286 (27.0)	41 (11.8)
Pregnancy-related infection	148 (26.7)	37 (17.6)	325 (28.6)	46 (12.5)
IUGR	99 (18.9)	90 (46.6)	221 (21.1)	25 (7.0)
Gestational age at delivery (weeks)				
24-25	110 (16.2)	22 (8.7)	180 (13.3)	104 (23.7)
26-27	144 (25.5)	55 (26.1)	282 (24.0)	98 (25.9)
28-30 ⁺⁶	291 (58.2)	123 (65.2)	632 (62.7)	164 (50.4)
Distance (km) to the closest level III unit, n (%)				
[0-6[251 (46.5)	61 (30.8)	194 (17.6)	44 (11.8)
[6-17[167 (29.9)	69 (34.4)	238 (21.7)	80 (22.2)
[17-48[106 (19.7)	47 (23.7)	283 (25.8)	107 (28.9)
≥48	21 (3.9)	23 (11.1)	379 (34.9)	135 (37.1)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes. IUGR: intrauterine growth restriction

Table 2: Risk factors for not delivering in level III maternity units in all women after multiple imputation.

Characteristics	Delivery outside level III unit [£] (%)	Unadjusted RR (95% IC)	Adjusted RR [§] (95% IC)
Maternal age. (years)			
< 25	21.8	1.39 (1.12,1.72)	1.19 (1.02,1.38)
25-34	15.7	1.00 (Reference)	1.00 (Reference)
≥35	12.0	0.76 (0.58,1.00)	0.93 (0.77,1.13)
Socioeconomic status			
Professional/Intermediate	13.5	1.00 (Reference)	1.00 (Reference)
Employee/worker	17.6	1.33 (1.06,1.66)	1.11 (0.94,1.30)
Not employed	21.3	1.73 (1.10,2.73)	1.19 (0.72,1.98)
Country of birth			
Birth out of France	12.1	0.70 (0.54,0.92)	1.11 (0.87,1.40)
France	17.3	1.00 (Reference)	1.00 (Reference)
Maternal comorbidity			
yes	11.9	0.73 (0.43,1.22)	1.42 (0.70,2.87)
no	16.4	1.00 (Reference)	1.00 (Reference)
Adverse obstetric history			
yes	17.5	1.09 (0.76,1.53)	0.90 (0.65,1.24)
no	16.0	1.00 (Reference)	1.00 (Reference)
Infertility treatment			
yes	10.8	0.64 (0.45,0.90)	0.70 (0.52,0.95)
no	16.9	1.00 (Reference)	1.00 (Reference)
Type of pregnancy			
Singleton	16.9	1.00 (Reference)	1.00 (Reference)
Multiple	12.8	0.75 (0.58,0.98)	0.81 (0.60,1.09)
Parity			
Nulliparous women	15.5	0.92 (0.76,1.14)	0.93 (0.80,1.07)
Multiparous women	16.8	1.00 (Reference)	1.00 (Reference)
Inadequate antenatal care			
yes	27.5	1.81 (1.37,2.38)	1.39 (1.10,1.81)
no	15.2	1.00 (Reference)	1.00 (Reference)
Preterm labour			
yes	22.6	1.89 (1.56,2.29)	0.97 (0.78,1.20)
no	12.0	1.00 (Reference)	1.00 (Reference)
PPROM			
yes	7.8	0.38 (0.30,0.50)	0.36 (0.28,0.46)
no	20.3	1.00 (Reference)	1.00 (Reference)
Haemorrhage			
yes	16.3	1.01 (0.80,1.29)	0.74 (0.58,0.95)
no	16.1	1.00 (Reference)	1.00 (Reference)
Placental abruption			
yes	27.7	1.82 (1.37,2.41)	1.66 (1.27,2.17)
no	15.2	1.00 (Reference)	1.00 (Reference)
HDP			
yes	8.1	0.44 (0.32,0.59)	0.40 (0.29,0.54)
no	18.6	1.00 (Reference)	1.00 (Reference)

Table 2 (Continued)

Characteristics	Delivery outside level III unit [£] (%)	Unadjusted RR (95% IC)	Adjusted RR [§] (95% IC)
Pregnancy-related infection			
yes	8.3	0.44 (0.33,0.59)	0.51 (0.37-0.70)
no	18.6	1.00 (Reference)	1.00 (Reference)
IUGR			
yes	5.4	0.29 (0.19,0.43)	0.31 (0.18,0.53)
no	18.9	1.00 (Reference)	1.00 (Reference)
Gestational age (weeks) at delivery			
24-25	25.0	1.49 (1.16,1.91)	1.37 (1.13,1.66)
26-27	16.8	1.00 (Reference)	1.00 (Reference)
28-30 ^{*6}	13.5	0.81 (0.64,1.02)	0.87 (0.75,1.01)
Distance to level III unit, (km).			
[0-6[7.6	1.00 (Reference)	1.00 (Reference)
[6-17[14.3	1.89 (1.33,2.70)	1.80 (1.35,2.41)
[17-48[18.9	2.50 (1.78,3.50)	2.39 (1.71,3.34)
≥48	23.6	3.11 (2.25,4.30)	2.79 (2.00,3.92)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes.

IUGR: intrauterine growth restriction. [£]Weighted percentages. [§] Multivariable GEE models (Region).

Table 3: Risk factors for not delivering in level III among women eligible for antenatal transfer after multiple imputation.

Characteristics	Delivery outside level III unit [£]	Unadjusted RR (95% IC)	Adjusted RR (95% IC) *
Maternal age. (years)			
< 25	31.5	1.35 (1.10,1.67)	1.14 (1.00,1.31)
25-34	23.9	1.00 (Reference)	1.00 (Reference)
≥35	18.9	0.76 (0.58,0.99)	0.92 (0.78,1.10)
Socioeconomic status			
Professional/Intermediate	20.9	1.00 (Reference)	1.00 (Reference)
Employee/worker	26.0	1.28 (1.04,1.57)	1.13 (0.97,1.31)
Not employed	37.6	1.95 (1.29,2.93)	1.42 (0.89,2.26)
Country of birth			
Birth out of France	20.5	0.80 (0.61,1.03)	1.17 (0.89,1.51)
France	25.5	1.00 (Reference)	1.00 (Reference)
Maternal comorbidity			
yes	21.4	0.87 (0.53,1.43)	1.60 (0.90,2.85)
no	24.5	1.00 (Reference)	1.00 (Reference)
Adverse obstetric history			
yes	29.1	1.21 (0.86,1.70)	0.94 (0.70,1.26)
no	24.1	1.00 (Reference)	1.00 (Reference)
Infertility treatment			
yes	16.4	0.65 (0.46,0.91)	0.69 (0.51,0.92)
no	25.6	1.00 (Reference)	1.00 (Reference)
Type of pregnancy			
Multiple	20.2	1.27 (0.98,1.65)	0.84 (0.66,1.07)
Singleton	25.4	1.00 (Reference)	1.00 (Reference)
Parity			
Nulliparous	22.6	0.85 (0.71,1.02)	0.94 (0.82,1.06)
Multiparous	26.7	1.00 (Reference)	1.00 (Reference)
Inadequate antenatal care			
yes	46.1	2.15(1.67,2.77)	1.57 (1.26,1.95)
no	22.9	1.00 (Reference)	1.00 (Reference)
Preterm labour			
yes	32.8	1.93 (1.60,2.33)	0.95 (0.82,1.10)
no	18.7	1.00 (Reference)	1.00 (Reference)
PPROM			
yes	11.8	0.40 (0.30,0.51)	0.35 (0.28,0.44)
no	30.9	1.00 (Reference)	1.00 (Reference)
Haemorrhage			
yes	25.9	1.10 (0.88,1.39)	0.77 (0.61,0.98)
no	24.0	1.00 (Reference)	1.00 (Reference)
Placental abruption			
yes	42.7	1.86 (1.43,2.43)	1.80 (1.49,2.17)
no	23.1	1.00 (Reference)	1.00 (Reference)
HDP			
yes	12.3	0.41 (0.30,0.55)	0.37 (0.28,0.50)
no	28.1	1.00 (Reference)	1.00 (Reference)

Table 3 (Continued)

Characteristics	Delivery outside level III unit [£]	Unadjusted RR (95% IC)	Adjusted RR (95% IC) *
Pregnancy-related infection			
yes	12.4	0.46 (0.34,0.61)	0.50 (0.37,0.67)
no	28.3	1.00 (Reference)	1.00 (Reference)
IUGR			
yes	9.6	0.28 (0.19,0.42)	0.40 (0.26,0.62)
no	27.6	1.00 (Reference)	1.00 (Reference)
Gestational age (weeks) at delivery			
24-25	36.6	1.51 (1.19,1.91)	1.42 (1.15,1.74)
26-27	25.8	1.00 (Reference)	1.00 (Reference)
28-30 ⁺⁶	20.6	0.79 (0.63,0.99)	0.88 (0.73,1.08)
Distance to level III unit, (km).			
[0-6[17.7	1.00 (Reference)	1.00 (Reference)
[6-17[24.8	1.45 (1.03,2.04)	1.29 (0.99,1.69)
[17-48[26.6	1.69 (1.22,2.33)	1.29 (1.02,1.63)
≥48	25.6	1.75 (1.28,2.40)	1.24 (1.01,1.52)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes.

IUGR: intrauterine growth restriction. [£]Weighted percentages.

[§] Multivariable GEE models (Region).

Table 4: Avoidable outborn delivery according to characteristics.

Characteristics	Delivery outside level III unit probably or possibly avoidable		Unadjusted RR (95% IC)
	N	%	
Maternal age. (years)			
< 25	80	36.3	0.84 (0.66,1.02)
25-34	185	45.5	1.00 (Reference)
≥35	52	32.6	0.78 (0.61,0.98)
Socioeconomic status			
Professional/Intermediate	91	38.4	1.00 (Reference)
Employee/worker	173	43.3	1.08 (0.88,1.33)
Not employed	13	58.0	1.46 (0.74,2.87)
Type of pregnancy			
Singleton	268	40.4	1.00 (Reference)
Multiple	49	52.6	1.25 (0.92,1.72)
Inadequate antenatal care			
yes	38	43.2	1.00 (0.74,1.35)
no	258	43.0	1.00 (Reference)
Preterm labour			
yes	171	43.8	1.02 (0.84,1.25)
no	134	42.4	1.00 (Reference)
PPROM			
yes	57	56.6	1.38 (1.01,1.90)
no	254	40.1	1.00 (Reference)
Haemorrhage			
yes	64	55.2	1.33 (0.99,1.79)
no	237	40.0	1.00 (Reference)
Placental abruption			
yes	39	25.8	0.73 (0.59,0.91)
no	273	45.6	1.00 (Reference)
HDP			
yes	39	53.3	1.26 (0.89,1.79)
no	278	40.7	1.00 (Reference)
Pregnancy-related infection			
yes	40	46.8	1.09 (0.80,1.49)
no	277	41.6	1.00 (Reference)
IUGR			
yes	22	65.7	1.73 (0.95,3.16)
no	295	40.5	1.00 (Reference)
Gestational age (weeks)			
24-25	87	51.7	1.47 (1.14,1.90)
26-27	85	28.9	1.00 (Reference)
28-30 ⁺⁶	145	44.8	1.29 (1.05,1.57)
Distance to level III unit, (km).			
[0-6[33	47.4	1.00 (Reference)
[6-17[70	42.9	0.99 (0.79,1.23)
[17-48[91	46.4	0.97 (0.78,1.21)
≥48	123	37.5	0.95 (0.76,1.18)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes. IUGR: intrauterine growth restriction.

eTable 1. Type of variable, model used to predict missing data, and percentages of values missing for each variable included in the Imputation model (N=2,205).

Variables	Type of variable	Model used to predict missing data	Percentages of values missing (%)
Maternal age	Categorical (3 categories)	Multinomial regression	<1
Socioeconomic status	Categorical (3 categories)	Multinomial regression	8
Country of birth	Binary	Logistic regression	9.8
Maternal comorbidity	Binary	Logistic regression	<1
Adverse obstetric history	Binary	Logistic regression	<1
Infertility treatment	Binary	Logistic regression	3.8
Type of pregnancy	Binary	Logistic regression	0
Parity	Binary	Logistic regression	1
Inadequate antenatal care	Binary	Logistic regression	5.9
Preterm labour	Binary	Logistic regression	1.4
PPROM	Binary	Logistic regression	<1
Haemorrhage	Binary	Logistic regression	2.7
Placental abruption	Binary	Logistic regression	1.4
HDP	Binary	Logistic regression	0
Pregnancy-related infection	Binary	Logistic regression	0
IUGR	Binary	Logistic regression	0
Gestational age (weeks) at delivery	Categorical (3 categories)	Multinomial regression	0

eTable 2: Sensitivity analyses - Risk factors of not delivering in level III maternity units in all women (complete cases - N=2,205).

Characteristics	n/N	Delivery outside level III units ^E (%)	Unadjusted RR (95% IC)	Adjusted RR* (95% IC)
Maternal age. (years)				
< 25	99/435	21.8	1.39 (1.12,1.72)	1.19 (1.02,1.38)
25-34	208/1,291	15.7	1.00 (Reference)	1.00 (Reference)
≥35	59/477	12.0	0.76 (0.58,1.00)	0.93 (0.77,1.13)
Socioeconomic status				
Professional/Intermediate	106/811	13.5	1.00 (Reference)	1.00 (Reference)
Employee/worker	198/1,141	17.6	1.33 (1.06,1.66)	1.11 (0.94,1.30)
Not employed	18/74	21.3	1.73 (1.10,2.73)	1.19 (0.72,1.98)
Country of birth				
Birth out of France	57/460	12.1	0.70 (0.54,0.92)	1.11 (0.87,1.40)
France	266/1,527		1.00 (Reference)	1.00 (Reference)
Maternal comorbidity				
yes	13/111	11.8	0.73 (0.43,1.22)	1.42 (0.70,2.87)
no	340/2,073	16.8	1.00 (Reference)	1.00 (Reference)
Adverse obstetric history				
yes	26/147	17.5	1.09 (0.76,1.53)	0.90 (0.65,1.24)
no	340/2,056	16.0	1.00 (Reference)	1.00 (Reference)
Infertility treatment				
yes	31/291	10.1	0.64 (0.45,0.90)	0.70 (0.52,0.95)
no	313/1829	16.6	1.00 (Reference)	1.00 (Reference)
Type of pregnancy				
Singleton	309/1,772	16.9	1.00 (Reference)	1.00 (Reference)
Multiple	57/433	12.8	0.75 (0.58,0.98)	0.81 (0.60,1.09)
Parity				
Nulliparous women	190/1184	15.5	0.92 (0.76,1.14)	0.93 (0.80,1.07)
Multiparous women	169/998	16.7	1.00 (Reference)	1.00 (Reference)
Inadequate antenatal care				
yes	44/150	27.5	1.81 (1.37,2.38)	1.39 (1.10,1.81)
no	293/1923	14.9	1.00 (Reference)	1.00 (Reference)
Preterm labour				
yes	188/860	22.6	1.89 (1.56,2.29)	0.97 (0.78,1.20)
no	155/1315	11.5	1.00 (Reference)	1.00 (Reference)
PPROM				
yes	61/762	7.8	0.38 (0.30,0.50)	0.36 (0.28,0.46)
no	292/1,425	19.9	1.00 (Reference)	1.00 (Reference)
Haemorrhage				
yes	73/456	15.8	1.01 (0.80,1.29)	0.74 (0.58,0.95)
no	269/1,688	15.4	1.00 (Reference)	1.00 (Reference)
Placental abruption				
yes	40/148	27.7	1.82 (1.37,2.41)	1.66 (1.27,2.17)
no	313/2,027	14.9	1.00 (Reference)	1.00 (Reference)
HDP				
yes	41/500	8.1	0.44 (0.32,0.59)	0.40 (0.29,0.54)
no	325/1,705	18.6	1.00 (Reference)	1.00 (Reference)
Pregnancy-related infection				
yes	46/556	8.3	0.44 (0.33,0.59)	0.51 (0.37,0.70)
no	320/1,649	18.7	1.00 (Reference)	1.00 (Reference)
IUGR				
yes	25/435	5.4	0.29 (0.19,0.43)	0.31 (0.18,0.53)
no	431/1,770	18.9	1.00 (Reference)	1.00 (Reference)

eTable 2 (Continued)

Characteristics	n/N	Delivery outside level III units [£] (%)	Unadjusted RR (95% IC)	Adjusted RR (95% IC)
Gestational age (weeks) at delivery				
24-25	104/416	25.0	1.49 (1.16,1.91)	1.37 (1.13,1.66)
26-27	98/579	16.8	1.00 (Reference)	1.00 (Reference)
28-30	164/1210	13.5	0.81 (0.64,1.02)	0.87 (0.75,1.01)
Distance to the closest level III unit, (km).				
[0-6[44/550	7.6	1.00 (Reference)	1.00 (Reference)
[6-17[80/554	14.3	1.89 (1.33,2.70)	1.80 (1.35,2.41)
[17-48[107/543	18.9	2.50 (1.78,3.50)	2.39 (1.71,3.34)
≥48	135/558	23.6	3.11 (2.25,4.30)	2.79 (2.00,3.92)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes. IUGR: intrauterine growth restriction. [£]Weighted percentages. *Multivariable GEE models (Region), missing data= 520.

eTable 3: Sensitivity analyses - Risk factors for not delivering in level III among women eligible for *in utero* transfer (complete cases - N=1,460).

Characteristics	n/N	Delivery outside level III units [£] n=366 (22.0%)	Unadjusted RR (95% IC)	Adjusted RR (95% IC) *
Maternal age. (years)				
< 25	99/303	31.5	1.32 (1.07,1.62)	1.14 (0.98,1.33)
25-34	208/853	23.9	1.00 (Reference)	1.00 (Reference)
≥35	59/303	18.9	0.79 (0.61,1.03)	0.78 (0.62,0.98)
Socioeconomic status				
Professional/Intermediate	106/524	19.7	1.00 (Reference)	1.00 (Reference)
Employee/worker	198/776	25.0	1.27 (1.02,1.56)	1.35 (1.13,1.63)
Not employed	18/42	39.1	1.97 (1.31,2.99)	1.38 (0.80,2.37)
Country of birth				
Birth out of France	57/279	19.5	0.78 (0.61,1.02)	1.06 (0.79,1.41)
France	266/1,041	24.8	1.00 (Reference)	1.00 (Reference)
Maternal comorbidity				
yes	13/62	21.3	0.89 (0.54,1.46)	2.29 (1.34,3.91)
no	340/1,382	23.9	1.00 (Reference)	1.00 (Reference)
Adverse obstetric history				
yes	26/89	29.1	1.20 (0.86,1.69)	0.99 (0.68,1.43)
no	340/1,371	24.1	1.00 (Reference)	1.00 (Reference)
Infertility treatment				
yes	31/192	15.4	0.61 (0.43,0.86)	0.60 (0.42,0.85)
no	313/1,212	25.2	1.00 (Reference)	1.00 (Reference)
Type of pregnancy				
Singleton	309/1,185	25.4	1.00 (Reference)	1.00 (Reference)
Multiple	57/275	20.3	0.80 (0.62,1.03)	0.82 (0.57,1.16)
Parity				
Nulliparous	190/811	22.5	0.85 (0.70,1.02)	0.91 (0.75,1.10)
Multiparous	169/634	26.4	1.00 (Reference)	1.00 (Reference)
Inadequate antenatal care				
yes	44/90	46.7	2.07 (1.62,2.64)	1.55 (1.24,1.95)
no	293/1,276	22.5	1.00 (Reference)	1.00 (Reference)
Preterm labour				
yes	188/591	31.4	1.75 (1.45,2.11)	0.93 (0.75,1.14)
no	155/844	17.9	1.00 (Reference)	1.00 (Reference)
PPROM				
yes	61/507	11.4	0.38 (0.29,0.49)	0.31 (0.24,0.40)
no	292/940	30.2	1.00 (Reference)	1.00 (Reference)
Haemorrhage				
yes	73/289	25.1	1.08 (0.87,1.36)	0.69 (0.55,0.87)
no	269/1,129	23.1	1.00 (Reference)	1.00 (Reference)
Placental abruption				
yes	40/97	42.0	1.86 (1.44,2.40)	1.90 (1.32,2.70)
no	313/1,340	22.6	1.00 (Reference)	1.00 (Reference)
HDP				
yes	41/327	12.3	0.44 (0.32,0.59)	0.22 (0.15,0.31)
no	325/1,133	28.1	1.00 (Reference)	1.00 (Reference)
Pregnancy-related infection				
yes	46/371	12.4	0.44 (0.33,0.58)	0.54 (0.39,0.78)
no	320/1,089	28.3	1.00 (Reference)	1.00 (Reference)

eTable 3 (Continued)

Characteristics	n/N	Delivery outside	Unadjusted RR	Adjusted RR
-----------------	-----	------------------	---------------	-------------

		level III units [‡] n=366 (22.0%)	(95% IC)	(95% IC) *
IUGR				
yes	25/246	9.6	0.35 (0.24,0.51)	0.50 (0.29,0.88)
no	341/1,214	27.6	1.00 (Reference)	1.00 (Reference)
Gestational age (weeks) at delivery				
24-25	104/284	36.6	1.41 (1.12,1.79)	1.34 (1.07,1.66)
26-27	98/380	25.8	1.00 (Reference)	1.00 (Reference)
28-30	164/796	20.6	0.80 (0.64,0.99)	0.88 (0.69,1.12)
Distance to the closest level III unit, (km).				
[0-6[44/238	17.7	1.00 (Reference)	1.00 (Reference)
[6-17[80/318	24.8	1.40 (1.00,1.95)	1.53 (1.20,1.94)
[17-48[107/390	26.6	1.49 (1.09,2.06)	1.50 (1.19,1.91)
≥48	135/514	25.6	1.44 (1.06,1.96)	1.60 (1.12,2.29)

HDP: hypertension disorders of pregnancy. PPROM: preterm premature rupture of membranes. IUGR: intrauterine growth restriction. [‡]Weighted percentages. *Multivariable GEE models (Region), missing data= 367.