Understanding geographic and temporal variations in preterm birth rates and trends : an international study in 34 high-income countries

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An international study in 34 high-income countries

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PhD dissertation in Epidemiology

Under the supervision of Jennifer Zeitlin

Defended publicly on Tuesday November 14th, 2017

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I dedicate this work to my parents, my sister and my daughter Annabelle, for their support and unconditional love,

Acknowledgements

First, I would like to thank my PhD advisor, Dr. Jennifer Zeitlin, Euro-Peristat project leader and Director of research at Inserm. You gave me this great opportunity in 2011 to join the unit and work with international maternal and child health data. Over the years, your kindness and leadership have been a real source of inspiration. I am forever grateful for your support and our collaboration.

I would also like to express my deepest respect to the members of the Thesis Committee: Dr. Catherine Arnaud, Dr. Isabelle Grémy, Dr. Anita Ravelli, and Prof. Damien Subtil. I am honored that you have accepted to review this doctoral work. Thank you for your availability and for being a part of this important moment in my life and my career.

I would like to acknowledge Prof. Dominique Costagliola, Head of the Pierre Louis Doctoral School of Public Health ED393. Thank you for your dedication to this School and for challenging its students to be daring in their research questions and rigorous in their methods. I will strive to use these skills in my future work.

I would like to acknowledge Prof. François Goffinet, Head of the Port Royal Maternity Unit and director of the EPOPé research team when it was known as INSERM U953. I have the deepest respect for your commitment to excellence in maternal and newborn health research and care.

My sincere thanks also go to Prof. Pierre-Yves Ancel, Head of the INSERM UMR1153 – EPOPé research team. Thank you for your kindness and your availability. I have the deepest respect for your dedication to preterm birth research and practice, and to the EPOPé research team. Please accept the assurance of my highest consideration.

I would like to thank Dr. Béatrice Blondel, Director of research at Inserm. Your thoughtful comments and our discussions have always encouraged me to improve the quality of my research. Thank you for your insight and your enthusiasm.

I would also like to acknowledge Mrs. Sophie Gouvaert, and Mrs. Nathalie Codet, administrators of the Inserm UMR1153- EPOPé research team. Thank you for your continued support over the years. You helped me carry out my work in the best conditions.

I would also like to thank Mrs. Lydie Martorana, administrator of the ED393 Doctoral Shool, for your availability and for organizing the doctoral seminars each year in St Malo.

I deeply thank all the members of the Euro-Peristat network, and the PREBIC group who participated in the collection and interpretation of data from 34 countries for this thesis. It has been a pleasure learning from you and finding out more about your national perinatal health care systems. Your contribution made this research possible.

I would like to thank the members of the Young Forum Gastein for broadening my horizons in european public health research, and for the friendships that were made. I look forward to working with you in the future.

Finally to my colleagues and friends, from the EPOPé research team. I feel very lucky to have conducted this work knowing that I could count on your kind words, your support and your advice. Thank you very much for all the great moments we have shared.

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Funding

This doctoral work was funded by Paris Descartes University for the period 01/10/2014 - 30/09/2017.

List of abbreviations

ART	Assisted Reproductive Technologies
BMI	Body Mass Index
ECHI	European Core Health Indicators
ETB	Early Term Birth
EU	European Union
GA	Gestational Age
MLP	Moderate and Late Preterm Births
OECD	Organisation for Economic Co-operation and Development
PTB	Preterm Birth
VPT	Very Preterm Birth
WHO	World Health Organisation

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Summary [in French]

Variations géographiques et temporelles des taux de prématurité : une étude comparative internationale dans 34 pays

Introduction

Chaque année, 15 millions d'enfants naissent prématurément, c'est-à-dire avant 37 semaines d'amenorrhées (SA), alors qu'une grossesse normale dure typiquement 39 à 41 SA. L'âge gestationnel à la naissance est utilisé comme marqueur de risque de morbi-mortalité et les grossesses les plus courtes sont celles les plus à risque. Les nourrissons les plus vulnérables sont les grands prématurés nés avant 32 semaines (38, 60), puis les enfants nés prématurés modérés entre 32 et 33 semaines, et tardifs à 34-36 semaines (6). Les naissances proche du terme, entre 37 et 38 SA, ne sont pas considérées comme prématurées, mais ces enfants font aussi face à un sur-risque de morbidité néonatale (4) et certains experts soulèvent la question de la limite d'âge gestationnel à utiliser dans la définition de la prématurité (19).

La prématurité constitue un enjeu de santé publique important. Globalement, elle est la seconde cause de décès chez les enfants de moins de 5 ans (16, 61), et contribue à environ 75% des décès néonatals et 60% des décès infantiles en Europe (16). Comparés aux enfants nés à terme, les prématurés font également face à un sur-risque d'handicaps moteurs et cognitifs durant l'enfance, et à l'âge adulte de maladies chroniques et de mort précoce (88, 94). Le coût sociétal de la prématurité est élevé, et lié à la prise en charge hospitalière en période néonatale(70) et à des dépenses ultérieures dans les secteurs de l'action sociale et de l'éducation (56).

Au cours des dernières décennies, la survie des enfants prématurés s'est améliorée, mais il y a eu peu d'avancées en terme de prévention. Les dernières recommandations françaises sur la prévention de la prématurité spontanée préconisent l'arrêt du tabac et l'utilisation d' interventions

(cerclage, progesterone) chez les femmes à haut risque de complications médicales, mais concluent que le niveau de preuves concernants d'autres stratégies préventives n'est pas suffisant (99). Chang et al. dans une étude internationale des pays à haut niveau de développement estiment que l'impact de la prévention (au vue des stratégies existantes) est limité à -5%(22).

En Europe, les taux de prématurité varient entre 5 et 11% (124) . Une telle hétérogénéité entre les pays avec des niveaux de développement similaires et des systèmes de santé comparables suggère que des réductions sont possibles. L'étude comparative des données internationales sur la prématurité pourrait permettre une meilleure évaluation des facteurs associés à des taux stables et faibles dans les pays; ceux-ci pourraient être ciblés par la prévention.

Objectifs et plan de la thèse

Afin de mieux appréhender les raisons qui sous-tendent les variations des taux de prématurité dans les pays à haut niveau de développement, nous avons tout d'abord synthétisé l'état des connaissances actuelles sur les déterminants populationnels de la prématurité. Ce travail nous a permis d'identifier trois axes de recherche. Nous avons étudié : 1) l'impact des différences d'enregistrement des naissances et des décès entre les pays, 2) l'impact des variations au sein d'autres sous-groupe d'âge gesationnel (AG), y compris proche du terme à 37-38SA, 3) et enfin le rôle des caractéristiques sociodémographiques et obstétricales des mères sur les variations des taux de la prématurité et la naissance proche du terme. Les résultats de nos analyses ont été intégrés aux chapîtres de la thèse, comme suit:

1. Une revue de la littérature sur les facteurs liés aux variations des taux globals de prématurité dans les pays Européens, publiée dans *Current Opinions in Obstetrics and Gynaecology* et disponible dans le chapître 2.

2. Une étude de la comparabilité des taux de grande prématurité à partir des données sur les naissances dans les systèmes d'information de 32 pays en 2010, publiée dans le *British Journal of Obstetrics and Gynaecology* et disponible dans le chapître 4

3. Une étude des variations des taux de prématurité en fonction des évolutions de la distribution des naissances par âge gestationnel dans 34 pays entre 1996 et 2010, publiée dans *l'European Journal of Public Health* et disponible dans le chapître 5.

4. Une analyse des caractéristiques maternelles en lien avec la prématurité et la naissance proche du terme à partir des données en France Métropolotaine en 2010, disponible dans le Chapître 6 et en cours de révision au *BMJ Open*.

Méthodes

Cette thèse utilise des données collectées par un réseau d'experts internationaux qui nous ont permis d'accéder aux statistiques officielles sur les naissances et les femmes enceintes dans 30 pays européens, les États-Unis, le Canada, le Japon et l'Australie de 1996 à 2010. Euro-Peristat, un projet européen sur la surveillance de la santé maternelle et infantile en Europe coordonné par l'équipe INSERM U1153-EPOPé nous a permis d'accéder aux données européennes ; tandis que le réseau PREBIC, une initiative sur la prévention de la prématurité soutenu par l'Organisation Mondiale de la Santé et la March of Dimes nous a permis d'obtenir les données d'Amérique du Nord et du Japon. Quant aux données Australiennes, celles-ci ont été collectées séparemment à partir du registre Médical des naissances du New South Wales. Toutes les données ont été compilées selon le protocole d'étude Euro-Peristat qui collecte ces indicateurs périnatals sur toutes les naissances vivantes et les décès à partir de 22 SA ou bien 500 g si l'âge gestationnel est manquant.

Concernant notre stratégie d'analyse, nous avons réalisé des analyses écologiques dans les Chapîtres 4 et 5 car nos données étaient aggrégées au niveau des pays et dans le temps; dans le chapître 6, nous disposions des données de l'Enquête National Périnatale 2010 sur l'ensemble de naissances en France pendant une semaine en 2010 et nous avons réalisé des analyses de régression multivariées. Des informations plus détaillées sur les méthodes utilisées et les analyses de sensibilité sont disponibles dans chacun des chapîtres de cette thèse. Par ailleurs, les données utilisées pour les analyses écologiques (la distributions des âges gestationnels dans les 34 pays en 1996, 2000, 2004, 2008 et 2010 pour les naissances vivantes uniques) ont été publiées en Annexe. Des informations supplémentaires sur les caractéristiques des sources de données utilisées dans chaque pays et par année sont aussi disponibles.

Revue des facteurs de risques de la prématurité dans les pays à haut niveau de développement

Nous avons ciblé les études permettant une comparaisons des facteurs de risques et des taux entre les pays, ou bien dans le temps au sein d'un même pays. Nous avons inclus les études les plus récentes (2011 à 2017) en provenance d'Europe, d'Amérique du Nord et d'Asie-Océanie. Nous avons identifié plusieurs facteurs associés aux variations géographiques et temporelles de la prématurité: la méthode d'estimation de l'âge gestationnel, le recours à l'aide médicale à la procréation, les caractéristiques des mères (sociodémographiques et comportementales), et certaines expositions environnementales (ie. qualité de l'air et pollution). Dans la littérature, un plus grand interventionnisme obstétrical et l'âge maternel avancé sont typiquement associés à la prématurité, mais les preuves les plus récentes sur l'influence de ces facteurs sont plus contrastées et semblent suggérer de nouvelles tendances. Cependant, la pluralité des étiologies de la prématurité (spontanée, ou induite par le practicien) complique l'interprétation de ces résultats.

Cette revue de la littérature nous a aussi amené à constater qu'il existe peu d'études internationales sur les facteurs de risque de la prématurité à l'échelle des pays, et celles-ci s'appuient souvent sur les mêmes zones géographiques. Zeitlin et al. ont comparé la France aux États-Unis (121), Garn et al. le Canada aux États-Unis (43), et Richards et al. les pays Nordiques (à savoir la Suède, la Norvège, le Danemark et la Finlande) aux États-Unis(87). Elargir ces analyses à d'autres pays permettrait d'obtenir une vision plus globale des obstacles et des opportunités pour la prévention.

Les caractéristiques intrinsèques des pays semblent contribuer aux taux de prématurité mais les résultats sont difficiles à synthétiser et soulèvent des problèmes méthodologiques. Les études que nous avons recensées ont intégré plusieurs facteurs de risques connus de la prématurité, mais n'arrivent pas à expliquer l'ampleur des variations observées dans les pays. Compte tenu des différences de mesure de l'AG et des pratiques d'enregistrement des naissances

et des décès dans les pays, il existe une incertitude concernant les méthodes et critères appropriés à utiliser dans les comparaisons internationales des taux de prématurité. De plus, les sources de données pour ces comparaisons sont souvent disparates, et les pays utilisent des groupes de référence différents pour les calculs de prévalence (toutes les naissances, naissances vivantes, naissances uniques).

Étude de la validité des comparaisons internationales des taux de prématurité à partir des sources de données en routine

Les critères d'inclusion des naissances dans les statistiques périnatales varient selon les pays. Par exemple, en France toutes les naissances à partir de 22SA sont enregistrées alors que la Suède utilise un seuil de 24SA pour les morts-nés, ou encore les Pays-Bas ne différencient pas les décés spontanés des interrruptions médicales de grossesses (IMG). Ces pratiques soulèvent des questions sur la validité des comparaisons internationales basées sur la mesure de l'âge gestationnel, en particulier pour les plus petits âges gestationnels. Dans cette étude, nous avons mesuré l'impact des naissances à 22-23 SA sur les taux de grande prématurité, selon les différentes pratiques d'enregistrement des naissances dans les pays.

Pour ce faire, nous avons utilisé des données agrégées sur les naissances vivantes et les décès avant 32 SA par mode d'accouchement dans 32 pays en 2010. Notre critère de jugement principal était le taux de grande prématurité défini par une naissance vivante ou un décès avant 32 semaines d'aménorrhée pour 1000 naissances totales, hors IMG si identifiable dans la source de données. Nous avons également utilisé les informations receuillies sur les pratiques d'enregistrement des naissances dans les systèmes d'information en routine. En 2010, les taux de grande prématurité variaient de 5,7 à 15,7 pour 1000 naissances totales, et de 4,0 à 11,9 pour 1000 naissances vivantes. Les pratiques d'enregistrement des pays étaient liées au pourcentage de naissances à 22-23 semaines de grossesse (entre 1% et 23% des naissances très prématurées), et aux décès (entre 6% et 40% des naissances très prématurées). Toutefois, en utilisant un seuil de 24 SA pour les calculs de prévalence, le rang des pays selon leur taux de grande prématurité

était globalement le même.

En conclusion, nous avons pu vérifier qu'il existe une grande variabilité des taux de grande prématurité à partir des données des systèmes d'information en santé des pays européens. Néanmoins, les naissances à 22-23 SA et les IMG sont à exclure des comparaisons internationales dû à des différences de pratiques d'enregistrements des naissances entre les pays. Ces résultats ont été publiés dans le *British Journal of Obstetrics and Gynecology (29).*

Étude des variations des taux de prématurité en fonction de la distribution de l'âge gestationnel

Ayant repertorié plusieurs facteurs de risques de la prématurité communs à toutes les grossesses (i.e. facteurs environnementaux, pratiques médicales) (chapitre 2) , et vérifié que les pratiques d'enregistrement n'expliquaient pas les différences observées entre les pays (chapitre 4), nous avons ensuite exploré le lien entre les taux de prématurité et l'ensemble de la distribution des naissances par AG. Plus précisément, nous avons émis l'hypothèse que les taux de prématurité pourraient être liés aux taux de naissances proche du terme (c'est-à-dire à 37-38 SA), car les enfants nés prématurés et proche du terme ont un plus grand risque d' issues néonatales défavorables, comparés aux enfants nés à 39 semaines et plus (19).

Nous avons utilisé des données sur l'âge gestationnel à la naissance chez les singletons nés vivants dans 34 pays / régions en 1996, 2000, 2004, 2008 et 2010. Nous avons mesuré la force des associations entre les taux de prématurité, et d'autres indicateurs de la distribution des naissances par AG: avec le taux de naissance proche du terme (à 37-38 semaines), et le terme moyen à la naissance. Pour ces analyses écologiques, nous avons utilisé des tests de corrélations de Pearsons ajustés, pour tenir compte du regroupement des taux par pays dans le temps.

En 2010, les taux de prématurité pour les naissances vivantes uniques variaient entre 4,1% et 8,2% (5,5% en moyenne) ; tandis que le taux médian de naissance proche du terme était de 22,2% mais variait entre 15,6% et 30,8% selon les pays. L'ampleur des variations pour ces deux sous-groupes d'AG était comparable, et variait du simple au double. En 2004, 2008 et

2010, les pays avec des taux de prématurité élevés ont enregistré des taux de naissances proche du terme plus élevés (r> 0,50, p <0,01). Les tendances dans le temps par sous groupe d'âge gestationnel étaient aussi fortement corrélées dans leur ensemble (ajusté-r = 0,55, p <0,01), et par mode d'accouchement. Les associations les plus récentes (en 2008 et 2010) étaient les plus marquées (Figure 1), et les résultats étaient similaires pour les naissances spontanées et induites.

Figure 1. Associations entre les taux de prématurité et les taux de naissance proche du terme en 1996, 2000, 2004, 2008, 2010 dans 34 pays.

D'après cette étude, les variations des taux de prématurité s'inscrivent au sein de plus grandes variations dans la distribution globale des naissances par AG. Les résultats publiés dans l'*European Journal of Public Health* semblent indiquer la présence de facteurs de risque communs aux naissances avant 39 SA. Ainsi, nous proposons d'élargir la population-cible de la prévention aux naissances avant 39SA, y compris celles à 37-38 SA. Ce travail apporte un nouveau point de discussion essentiel dans l'élaboration des futures stratégies de prévention de la prématurité.

Identification des déterminants de la prématurité et de la naissance proche du terme en France

Dans les analyses précédentes, nos données étaient aggrégées ce qui ne permettait pas l'identification des facteurs de risque spécifiques à l'accouchement prématuré ou proche du

terme dans les 34 pays, cependant nous avons pu accéder à des données sur un échantillon représentatif des naissances en France pour explorer cette question. A partir des données de l'Enquête Nationale Périnatale (ENP) 2010, nous avons effectué des analyses de régression multinomiale. Nous avons mesuré l'influence des caractéristiques sociodémographiques, anthropométriques et obstétricales des femmes sur la prématurité et l'accouchement proche du terme, car selon les résultats de l'étude précédente ces deux issues de grossesse pourraient bénéficier de stratégies de prévention conjointes.

Nous avons estimé le risque de prématurité (<37SA) ou de naissance proche du terme (37-38 SA) pour chaque caractéristique maternelle, en utilisant comme groupe de référence toutes les naissances à 39 SA ou plus. Nous avons inclus dans notre modèle statistique les caractéristiques maternelles suivantes: l'âge, le niveau d'études, la nationalité, les antécédents obstétricaux (prématurité et parité), la taille, l'IMC avant grossesse et le tabagisme. Les variables ont été choisies selon leur disponibilité dans l'ENP 2010, et notre revue de la littérature. Cependant, nous n'avons pas pu inclure certains facteurs connus de la prématurité dont la prévalence était faible dans notre échantillon (i.e. hypertension, FIV, diabète). Enfin, nous avons réalisé nos analyses de manière globale et selon le mode de déclenchement de l'accouchement (i.e. spontané ou induit).

En France, le taux de prématurité pour les naissances vivantes uniques était de 5.5%, et 22.5% pour les naissances proches du terme. Nous avons identifié plusieurs facteurs de risque communs aux naissances avant 39 SA dont: un antécédent de prématurité (aOR = 8,2 pour une naissance prématurée, et proche du terme aOR = 2,4), une petite taille, la maigreur, l'obésité, un faible niveau d'études, et une origine étrangère. D'autres facteurs étaient différents. Les primipares étaient essentiellement à risque de prématurité, tandis que la grande multiparité était associée à une plus grande probabilité de naissance proche du terme. Enfin deux facteurs étaient peu liés à nos issues principales: le tabac et l'âge maternel. Ce travail est en cours de révision

dans le *BMJ Open.*

Synthèse et nouvelles perspectives pour la prévention

Pour résumer, ce travail doctoral met en évidence une réelle hétérogénéité des taux de prématurité à partir des sources de données en routine dans 34 pays de 1996 à 2010. Les différences d'enregistrement des naissances dans les pays à revenus élevés ont un impact limité sur les variations des taux de prématurité, sauf pour les naissances à 22-23 SA. Nous avons également démontré que les évolutions des taux de prématurité accompagnent des modifications plus globales dans la distribution des naissances par AG. En France, les facteurs de risques maternels étaient pour la plupart les mêmes pour la prématurité et la naissance proche du terme ce qui suggère qu'il pourrait y avoir un continuum de la prématurité et une origine étiologique commune aux naissances avant 39SA.

Ces résultats ont des implications pour la mise en place et l'évaluation des programmes de prévention de la prématurité. Typiquement, la prévention de la prématurité dépend d'interventions qui ciblent les grossesses sur des critères cliniques (un col de l'utérus raccourci ou une hypertension maternelle), malgré la faible précision des outils diagnostiques de la prématurité (22). Dans leur ensemble, ces programmes semblent avoir peu d'impact, et en France la prématurité a même augmenté de 4,5% en 1995 à 6,0% en 2010 pour les naissances vivantes uniques. De nouvelles approches préventives sont à explorer (84) ; le paradigme de prévention que nous proposons élargit l'éventail des interventions aux naissances à 37-38 semaines. De plus, un résultat important de nos recherches est qu'en France, il faudrait diminuer la prématurité en agissant entre autres sur plusieurs déterminants non-médicaux de la santé (i.e. statut socioéconomique des femmes). L'implémentation de politiques qui permettraient une meilleure intégration des femmes d'origine étrangère ou avec un niveau d'étude faible requiert un partenariat renforcé entre les différents acteurs de la santé: décideurs de politiques publiques, cliniciens et usagers ainsi qu'une approche plurisectorielle en amont, et durant la grossesse. Par ailleurs, il serait utile d'analyser les sources de données individuelles

d'autres pays pour identifier les déterminants d'un accouchement précoce avant terme complet (à 39-41 SA) dans d'autres contexte nationaux, notamment concernant les expositions sociodémographiques et environnementales.

Pour conclure, viser à réduire les facteurs de risques de la naissance proche du terme et de la prématurité dans une approche conjointe pourrait apporter un nouvel élan à la prévention de la prématurité. Les naissances avant 39 SA, représentent entre 20 et 40% des naissances dans les pays. Comparés aux enfants prématurés, les enfants nés proche du terme à 37-38 SA sont individuellement moins à risque, mais à l'échelle des pays ces enfants contribuent de manière importante au fardeau de morbi-mortalité néonatale et infantile car ils sont nombreux (23% vs 7% pour les naissances vivantes en France). Au niveau national, élargir les efforts de prévention à cette nouvelle population-cible pourrait avoir un plus grand impact sur la santé publique.

Mots clés : prématurité, naissance proche du terme, terme précoce, distribution de l'âge gestationnel, prévention en population, surveillance de la santé, information en santé, Euro–Peristat

Summary

Preterm birth (PTB), defined as birth before 37 weeks, is a leading cause of infant mortality and morbidity. Compared to term infants, preterm infants face important risks of motor and cognitive impairments throughout childhood, as well as chronic diseases and premature death later in life. PTB represents a significant public health burden and in Europe, rates range between 5 and 10%. Such wide differences suggest that reductions may be possible, but there are few effective interventions, and these tend to target selected groups of high-risk pregnancies, based on clinical risk factors. Our aim for this thesis was to better appraise sources of population-level PTB rate variations and trends.

First, we conducted an exhaustive review of the literature and found that maternal characteristics, reproductive policies, medical practices and methods of gestational age (GA) estimation affected PTB rates, but could not explain observed differences across countries. Next, using population-based data on pregnant women, newborns and stillbirths in 34 high-income countries from 1996 to 2010, we showed that: 1) reporting criteria for births and deaths affected PTB rates at early gestations and PTB rankings, but differences between countries with high and low rates are not just due to artefact 2) PTB trends were associated with broader shifts in countries' gestational age GA distribution of births, and 3) using data from a representative sample of births in France in 2010, that there were shared maternal prenatal and socio-demographic risk factors for deliveries that did not reach full term, at 39 weeks GA. Our work confirms that recording differences in high-income countries have a limited impact on PTB rate variations. However, a broader focus on earlier delivery, including early term birth at 37-38 weeks, could shed light on the determinants of low PTB rates and provide a useful public health prevention paradigm. **Keywords:** preterm birth, early term birth, gestational age distribution, population prevention, perinatal health surveillance, health information, Euro-Peristat

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Invited presentations

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28th Society for Pediatric and Epidemiologic Research SPER Annual meeting, 15-16 June 2015, Denver, USA: "Variations in very preterm births rates in Europe: can valid comparisons be made using routine data?" M Delnord**, AD Hindori-Mohangoo, LK Smith, et al.

*oral presentation **poster presentation

Chapter 1: Introduction

1. Background

The typical length of pregnancy is 39 to 40 completed weeks of gestation, but each year 15 million children are born preterm, before 37 completed weeks of gestation. Gestational age (GA) subgroups among preterm births are used as a marker of mortality and morbidity risk (6). The earlier the birth, the higher the odds of adverse health outcomes. The most vulnerable infants are those born very preterm between 22 and 31 completed weeks of gestation (38, 60). Those born between 32-33 weeks are known as moderate preterm, and births at 34-36 weeks are late preterm (16). Early term births, at 37 and 38 weeks are not considered preterm birth, but compared to infants born before 39 weeks, these infants are also increasingly shown to have high risk of neonatal care intensive care unit admission, and higher health-related costs well into childhood (4).

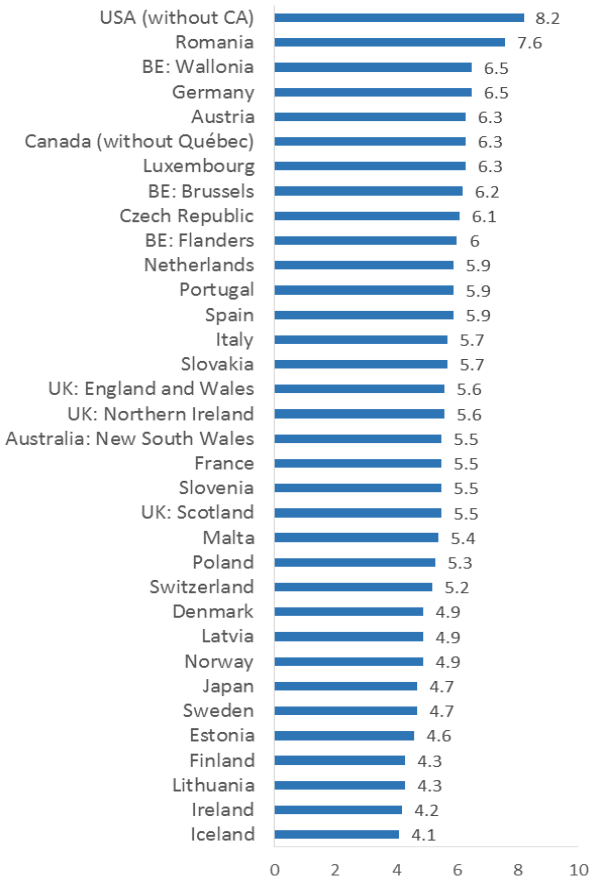
Prematurity contributes greatly to adverse perinatal events globally: it claims the lives of 1 million children annually, and it is the second leading cause of under-5 mortality (33, 61). Although survival of preterm infants has increased over the past decades, in Europe these births still represent about 75% of all neonatal deaths, and 60% of all infant deaths (16). For survivors, neonatal morbidity rates are high due to increased risks of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage, compared to term births (16, 33, 61). Later in life, preterm infants are also more inclined to suffer from long term motor and cognitive impairments, chronic disease and early death (16, 26, 88, 94). In the UK, the estimated cost for all preterm infants until the age of 18 years old is £3Billion. Expenses are largely incurred as hospital inpatient costs after birth (40, 70, 94, 96) but these can also carry over to other sectors such as education and social care throughout the life course (56)(97).

There are multiple clinical risk factors associated with PTB. These have been well described and include: a previous preterm birth, multiple pregnancy, infection, inflammation, hypertensive and vascular disorders, diabetes, a shortened cervix, placentation disorders, and the use of assisted reproductive therapies (12, 42). Yet, the specific physiological pathways leading to preterm delivery have not been identified (91, 114). Two-thirds of preterm births occur spontaneously following preterm labor or premature rupture of membranes(46), but providers also induce preterm delivery for fetal reasons, such as growth restriction, or when the mother's health is at stake, as for severe preeclampsia (12). At this time, there are no reliable biomarkers that can predict preterm birth risk and for more than half of all preterm births the biological cause is unknown(36, 82).

While prevention of preterm birth is an important public health goal, national public health programs struggle to reduce global rates (22, 91, 102). Prevention could yield substantial gains for instance in the reduction of associated mortality, in-patient costs and quality of life (i.e. each 100 averted preterm births could represent an estimated $5M in savings for the US healthcare system (22)), but medical interventions such as progesterone supplementation and cerclage can help delay the onset of labor in some *high-risk* pregnancies, but not all (3, 76, 113). Moreover, tocolytic drugs which inhibit uterine contractions delay PTB by hours or a few days only (50). The latest French recommendations for the prevention of spontaneous preterm birth focus on smoking cessation, and on clinical interventions for women with high-risk pregnancies (i.e. cerclage, progesterone) but conclude that high quality evidence does not exist for other preventive strategies (100) - this is partially due to the low predictive accuracy of diagnostic tools (22). Overall, existing strategies have shown limited potential in reducing global preterm birth rates: an estimated 5% relative rate reduction in high-income countries (22).

In 2010, live singleton PTB (<37 weeks) varied between lows of 4.1-4.3% in Iceland, Ireland, Lithuania, and Finland to highs of 7.6-8.2 % in Romania and the United States (cf. Figure 1); this corresponds to a 50% excess in countries with higher versus lower rates (2). While worldwide preterm birth rates have increased in general over the past decade, country specific trends are heterogeneous and vary by subgroup (17). In particular, rates of singleton preterm birth have been stable or declined in about half of European countries over the past 15 years, and the reasons for this are unknown; there were also wide differences in both spontaneous and indicated preterm birth (124). In 2010, live very preterm birth rates (<32 weeks) ranged between lows of 0.7% and 0.8% in Iceland, Malta and Finland and highs of 1.3% and 1.4% in Austria, Germany, Belgium: Brussels and Germany(2). Rates for multiples ranged between 39.6% and 66.9% (2).

Figure 1 Percentage of live births with a gestational age<37 weeks in 2010 in 34 countries



Note: In the USA, births from California were excluded due to non-reporting of clinical estimates.

Heterogeneity in preterm birth rates and trends provides an opportunity to gain further insight on the etiology of early delivery. In countries with similar levels of development and comparable health care systems, differences in the proportion of pregnancy complications are too small to explain wide differences in PTB rates (102). Instead, there may be intrinsic variation in population characteristics which could also impact on pregnancy length. Differences in medical approaches and the management of complications of pregnancy may also play a role. Evaluating how some populations have maintained low and stable PTB rates while others have not may be one approach to orienting prevention strategies and marshaling stakeholders.

Analyses of trends in time and cross-country comparisons can help initiate the identification of these mechanisms but there are obstacles to comparative research and monitoring. For one, preterm birth data are not available in routine international statistics. While the OECD and Eurostat produce statistics on maternal and child mortality, preterm birth is not included among their indicators. As for the WHO[1], it collects data on the percent of low birth weight infants under 2500g but not on preterm birth. Moreover at the national level, preterm birth rates may be available but there are differences in measurement and registration criteria across countries which can limit their use (45). Observational studies have the same shortcomings, and few studies report data by GA subgroups, multiplicity, or by mode of onset of delivery (2, 17, 22, 36, 58, 87, 124). On the other hand, the European surveillance and research network, Euro-Peristat, collected population-based data on PTB and compiles data on the GA distribution of births across countries; this constitutes an opportunity to explore sources of intenational variation in PTB rates, and within countries over time.

[1] WHO-Health for all database: Source: http://www.euro.who.int/en/data-and-evidence/databases/european-health-for-all-family-of-databases-hfa-db

2. Work plan

This doctoral work stems from a joint collaboration between the Euro-Peristat project, an EU-funded projet that compiles perinatal health indicators in 31 European countries, and the Preterm Birth International Collaborative Epidemiology Working Group (PREBIC), a global WHO initiative on preterm birth prevention. Our aim for this thesis was to investigate geographic and temporal variations in preterm birth rates in high-income countries from Europe, North America, and Asia-Oceania using data from routine population-based data sources, as collected by Euro-Peristat. We also analyzed data using a French random sample of births to explore the hypotheses raised by these cross-country analyses. More specifically, we carried out four studies, corresponding to the publications in this manuscript:

1) A review of the literature to identify population-level PTB risk factors that could explain differences between countries

The scoping review of the literature on the determinants of global preterm birth rates in high-income countries is presented in Chapter 2.

2) A study to identify the impact of registration practices for births and deaths on international PTB comparisons using data from routine health information systems

There are large differences in recording practices for births at the limits of viability and for stillbirths which raise questions about the comparability of preterm birth estimates, and other perinatal health indicators derived from the gestational age distribution of births. In Chapter 4, we provide practical recommendations for comparisons of very preterm birth rates, including a methodology to flag countries where recording practices may influence preterm birth rankings.

3) An analysis of the associations between preterm birth rates and broader indicators of the gestational age distribution of births:

Using across country and time trend analysis data from 34 countries and regions in 5 time points between 1996 and 2010, we examined the associations between the preterm birth and early term birth rates in 34 countries. This work is presented in Chapter 5.

4) A study to explore population risk factors for early delivery before full term at 39 weeks in France.

Based on our findings in Chapter 5 of common patterns of preterm and early term birth in our international dataset, we decided to further assess shared population risk factors for preterm and early term birth in France. We used multinomial regression analyses to determine the odds of preterm (< 37 weeks) and early term (37-38 weeks) delivery compared to full term birth (39-40 weeks) by maternal characteristics.

In the final chapter and to conclude our work, we summarize our findings and we relate the impact of our work to key stakeholders' needs. We discuss the importance of measurement and registration differences, shifts in the overall gestational age distribution and baseline risk exposures, and potential target exposures for the prevention of early delivery. In recent years, there has been a major push for the harmonization of health information systems in European countries, and in line with these efforts, we suggest ways in which our findings could inform perinatal health surveillance. In addition, we highlight potential links across public health initiatives to decrease the medicalization of childbirth and the burden of preterm delivery.

Chapter 2: State of the art

At the onset of this doctoral project, we reviewed the most recent literature on potential sources of preterm rate variations between countries. We included studies from Europe and from Canada, Australia, Japan, and the United States. We scoped population-based studies reporting specifically on differences between countries or over time within countries. We restricted our search to studies published during the past five years (2011-2014). Our literature review is focused on population characteristics, reproductive policies as well as medical practices which may affect preterm birth rates.

It was published in February 2015 under the following citation:

Delnord M, Blondel B, Zeitlin J. What contributes to disparities in the preterm birth rate in European countries? Curr Opin Obstet Gynecol. 2015 Feb 17.2015 Apr; 27(2):133-42.

In the second part of this chapter, we highlight new and important findings from 2014-2017.

OPEN

What contributes to disparities in the preterm birth rate in European countries?

Marie Delnord, Béatrice Blondel, and Jennifer Zeitlin

Purpose of review
In countries with comparable levels of development and healthcare systems, preterm birth rates vary markedly – a range from 5 to 10% among live births in Europe. This review seeks to identify the most likely sources of heterogeneity in preterm birth rates, which could explain differences between European countries.

Recent findings
Multiple risk factors impact on preterm birth. Recent studies reported on measurement issues, population characteristics, reproductive health policies as well as medical practices, including those related to subfertility treatments and indicated deliveries, which affect preterm birth rates and trends in high-income countries. We showed wide variation in population characteristics, including multiple pregnancies, maternal age, BMI, smoking, and percentage of migrants in European countries.

Summary
Many potentially modifiable population factors (BMI, smoking, and environmental exposures) as well as health system factors (practices related to indicated preterm deliveries) play a role in determining preterm birth risk. More knowledge about how these factors contribute to low and stable preterm birth rates in some countries is needed for shaping future policy. It is also important to clarify the potential contribution of artifactual differences owing to measurement.

Keywords
cross-national comparisons, Euro-Peristat, preterm births, trends

INTRODUCTION

Preterm birth, defined as birth before 37 weeks of gestation, is a major cause of neonatal and infant mortality [1▪▪,2]. In Europe, about 75% of all neonatal deaths and 60% of all infant deaths occur to infants born preterm [1▪▪]. Although survival of preterm infants has increased significantly in the past decade, these infants remain at higher risks of long-term motor and cognitive impairments as well as of chronic disease and mortality later in life than infants born at term [3,4]. Initiatives to prevent preterm births have had limited success [5,6].

In countries with comparable levels of development and healthcare systems, preterm birth rates vary markedly – a range from 5 to 10% among live births in Europe [7▪▪,8,9▪▪]. Why these disparities exist is poorly understood, yet this knowledge is invaluable for orienting health policy and prevention initiatives. This review thus seeks to identify the most likely sources of heterogeneity in preterm birth rates, which could explain differences between European countries. Drawing on the most recent literature and in the light of data from the 2013 European Perinatal Health Report [1▪▪], our review focuses on population characteristics, reproductive policies as well as medical practices, which may affect preterm birth rates.

SEARCH STRATEGY AND SOURCES

We searched PubMed for publications between 2011 and 2014, which focused on explaining differences in preterm birth rates between countries in Europe.

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Curr Opin Obstet Gynecol 2015, 27:133–142

DOI:10.1097/GCO.0000000000000156

KEY POINTS

- Medical practices and policies related to subfertility treatments and indicated preterm deliveries have a clear impact on country-level preterm birth rates and trends.
- Recent studies confirmed the role of many potentially modifiable population factors – BMI, smoking, and environmental exposures – in determining preterm birth risk.
- It is important to rule out gestational age measurement artifacts.

Because we could not identify recent studies looking at this issue, we enlarged our search to studies from other high-income countries, including Australia, Canada, Japan, and the United States. Our assumption is that results from these contexts are relevant to European populations. We also extended our review to include studies that have evaluated the impact of specific risk factors on population-level preterm birth rates or trends in preterm birth rates within countries. Last, we used data from the Euro-Peristat project, which aims to monitor perinatal health using a recommended set of national-level indicators derived from routine systems [1▪▪]. These data illustrate the variability in specific risk factors for preterm birth across Europe and the extent to which preterm birth rate variations across countries may reflect differences in their prevalence. The 2013 Euro-Peristat report presented 2010 data from 29 countries on the preterm birth rate and factors affecting preterm birth risk such as: multiple births, maternal age, prepregnancy BMI, smoking during pregnancy, and migration status, which we compiled for this review (Table 1).

PRETERM BIRTH RATES IN EUROPE

In Europe, preterm birth rates for live births varied in 2010 between 5.2–5.9% in Iceland, Finland, Lithuania, Estonia, Latvia, Sweden, and Ireland and 8.2–10.4% in Belgium, Austria, Germany, Romania, Hungary, and Cyprus as illustrated in Fig. 1 and Table 1. This corresponds to a 50% excess in countries with higher vs. lower rates and corresponds to a 3 percentage-point absolute difference (Fig. 1). Although overall rates have increased in general, as reported by a World Health Organization (WHO) study of preterm birth in 64 countries [8], trends are heterogeneous and, in particular, rates of singleton preterm birth have been stable or declined in about half of European countries over the past 15 years [9▪▪].

MEASUREMENT

Measurement of gestational age is a potential source of variation between countries [10]. Timing of the first day of the mother's last menstrual period (LMP) or biometric measures from ultrasound (US) can be used to establish the first day of the pregnancy. The method of determining gestational age influences estimates of the preterm birth rate [5]. US dating tends to shift all pregnancies toward earlier gestational ages [10,11▪] mainly because LMP dating assumes that all women have a 28-day cycle, whereas in reality, average cycle length is slightly longer [12]. However, US removes errors in gestational age estimation and these corrections reduce the preterm birth rate because errors have more influence at the extremes of the distribution. The algorithms used to derive gestational age when LMP and US are both available will also affect the preterm birth rate [10]. Another potential source of variation between countries may be the references for US dating, as these are not standardized [13]. Finally, population characteristics influence gestational age measurement and vary across healthcare systems; socially disadvantaged women have less accurate dates [10,14,15▪], which may reflect difficulties in accessing prenatal care

In Europe, prenatal care starting in the first trimester is the norm and the 'best obstetric estimate' is the standard for pregnancy dating, although information on how this estimate is derived is not available in international databases [1▪▪,11▪,16▪▪]. Some routine data systems, such as in Norway and Sweden, record both LMP and the US estimate. In the United States, official preterm estimates are mainly based on LMP, but the clinical/obstetrical estimate is also recorded [11▪,17,18]. The use of LMP vs. clinical estimates explains half of the difference between United States and Canadian rates (12.3 vs. 7.6%, respectively in 2002) [19]. We could not find recent European studies about how gestational age measurement affects the preterm birth rate.

Differences in the registration of births and deaths at 22 and 23 weeks of gestation are highly problematic for international comparisons of perinatal and infant mortality [20,21▪], but their effect on overall preterm birth rates is probably small: in 2010, only 0.1% of live births in the countries included in Table 1 were born at 22–23 weeks [1▪▪]. These differences will, however, have a larger impact on comparisons of very preterm birth rates.

MULTIPLE PREGNANCIES

Increasing multiple birth rates, starting in the 1980s, have contributed to overall rises in preterm birth rates [22,23]. In 2010, preterm birth rates for

Table 1. Preterm birth rates and prevalence of maternal risk factors in European countries in 2010

Country	Live births (*N*)	PTB[a] (%)	Multiple births (%)	Stand PTB[b] (%)	<20 years of age (%)	>35 years of age (%)	Foreign born[c] (%)	Smoking during pregnancy (%)	BMI <18.5 (%)	BMI ≥30 (%)
Austria	78698	8.4	3.5	8.3	3.2	19.7	29.3			
BE: Brussels	24860	8.4	4.5	7.8	2.0	23.2	66.2		5.7	10.4
BE: Flanders	69637	7.9	3.8	7.7	1.8	14.3	22.4		5.3	12.4
BE: Wallonia	38228	8.3	3.3	8.3	3.8	16.0	25.2		7.1	13.6
Cyprus (2007)	8575	10.4	5.4	9.2	1.9	15.5	32.7			
Czech Republic	116399	8.1	4.1	7.7	2.9	15.4	2.6	6.2		
Denmark	63273	6.4	4.1	6.1	1.4	20.9	15.2	12.8	6.8	12.6
Estonia	15816	5.6	2.9	5.8	2.3	20.7	24.9	7.8		
Finland	61191	5.7	3.1	5.7	2.3	18.0	6.2	1.0	3.6	12.1
France	14761	6.5	3.0	6.7	2.5	19.2	18.3	17.1	8.3	9.9
Germany	635561	8.4	3.7	8.1	2.1	23.6	16.9	8.5	3.6	13.7
Hungary	90322	8.9	NA	NA	5.9	17.5	NA			
Iceland	4886	5.2	2.8	5.4	3.1	19.1	12.1			
Ireland	75243	5.7	3.4	5.7	2.7	27.9	24.6			
Italy	544991	7.3	3.2	7.4	1.4	34.7	19.0			
Latvia	19139	5.8	2.5	6.1	5.9	14.7	30.2			
Lithuania	30831	5.4	2.6	5.7	3.8	14.9	12.8	4.5		
Luxembourg	6519	8.1	3.6	8.0	1.8	23.3	66.0	12.5		
Malta	4018	7.2	4.0	6.9	6.5	15.5	9.2		5.2	12.7
Netherlands	177817	7.5	3.4	7.4	1.4	21.6	21.1	6.2		
Norway	62678	6.2	3.3	6.2	2.2	19.5	24.8	7.6	4.1	12.2
Poland	413295	6.6	2.7	6.8	4.5	11.8	0.04	12.3	8.7	7.1
Portugal	101463	7.7	3.0	7.8	4.0	21.7	19.0			
Romania	212199	8.2	1.8	8.7	10.6	10.9	NA			
Slovakia	55645	7.1	2.9	7.3	7.3	12.6	NA			
Slovenia	22298	7.2	3.7	7.1	1.2	15.4	NA		4.7	9.0
Spain	398914	8.0	4.2	7.5	2.5	29.5	23.6	14.4[d]		
Sweden	114706	5.9	2.8	6.1	1.6	22.5	24.4	4.9	2.5	12.6
Switzerland	79931	7.1	3.7	6.9	1.1	25.8	41.1			
UK: England & Wales	718266	7.0	3.1	7.1	5.7	19.7	25.2	14.0[e]		
UK: Northern Ireland	25586	7.1	3.1	7.2	5.1	19.9	13.5	15.0		
UK: Scotland	57151	7.0	3.1	7.1	6.4	19.9	13.9	19.0	2.6	20.7
United Kingdom	799 082				5.7	19.7	24.0	12.0		
Total	4252575									

Source: European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010 [1▪▪].
[a]PTB: preterm birth rate, defined as birth before 37 completed weeks of gestation.
[b]Stand. PTB: standardized preterm birth rate – adjusted on the prevalence of multiple births.
[c]Mothers born outside of the host country or of foreign nationality at birth (in Italy, Latvia, Lithuania, Malta, Poland) or ethnicity (in Denmark, Germany, Estonia) if data were unavailable.
[d]Data are from Catalonia.
[e]Average rate for UK: England (12.0%) and UK: Wales (16.0%).

multiples in Europe ranged between 39.6 and 66.0%, in contrast with between 4.1 and 7.6% for singletons [1▪▪]. Multiple birth rates vary from about 2 to 4% of all births, as shown in Table 1.

Variation in multiple birth rates is related to the proportion of older mothers who have more spontaneous multiple pregnancies and a greater demand for fertility treatments. It is also related

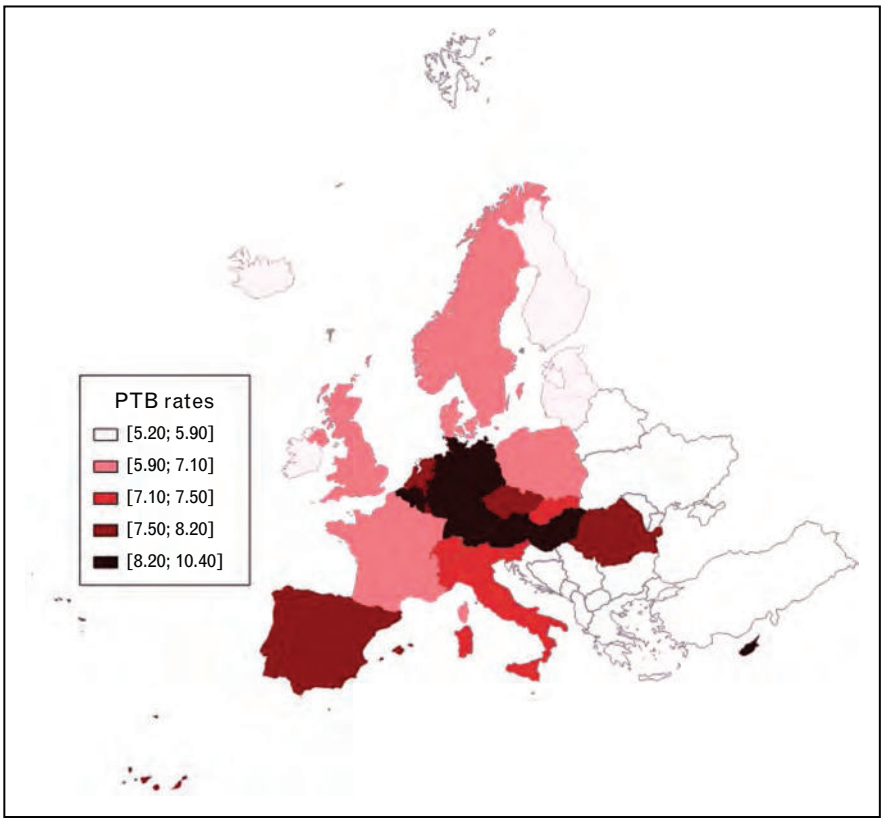

FIGURE 1. Rates of preterm birth (PTB) among live births in Europe in 2010.

to subfertility treatment policies and practices (in-vitro fertilization, ovulation induction and inseminations), which differ across high-income countries [24,25▪,26▪▪]. For instance, elective single embryo transfer (eSET) has been extensively promoted by several countries including Belgium, Sweden, Finland, and Australia [24,25▪,27]. In contrast, in Italy, the law requires transfer of all fertilized embryos in each cycle, although it limits the number of fertilized embryos to three [28]. Recent studies comparing use of eSET across countries showed a clear impact on multiple births [25▪,26▪▪]. eSET policies in Slovenia were credited with the stabilization of the proportion of assisted reproductive technology (ART) very preterm twins in past years after a 27-fold increase from 1987 to 2010 [29].

One source of heterogeneity between countries could thus be multiple births. To assess their contribution, we recomputed preterm birth rates assuming that all countries had the same multiple birth rate (set at the European average of 3.2%), as shown in Table 1. Substantial variability persists after this adjustment, although standardized rates are over half a percentage point lower in some countries. Larger declines occur more often in countries with high rates.

CHARACTERISTICS OF THE POPULATION OF CHILDBEARING WOMEN

Maternal characteristics associated with preterm delivery risk include age, socioeconomic status, migration status, BMI, smoking, drug use and alcohol consumption, occupational exposure, short interpregnancy intervals, previous preterm birth, preexisting medical conditions, ART use, and previous induced abortions [30,31▪▪,32▪▪,33–36]. It is hard to obtain European-level data on the prevalence of many of these risk factors, but as shown in Table 1, those available in the Euro-Peristat project clearly differ between countries, including maternal age, migrant status, smoking, and BMI. Articles included in our review addressed maternal age, social status, migration, smoking, obesity, diet, and previous induced abortion.

In 2010, the proportion of mothers 35 years of age and older in European countries ranged between 11 and 35% (Table 1); given that older women face higher risks of preterm birth, this could be one explanation for country-level differences. Auger *et al.* [37▪▪] tested the hypothesis that advancing maternal age may be a cause of rising preterm birth rates. In a study comparing singleton births in Denmark and Quebec, where preterm birth rates rose over the past 15 years, they found that rates

had increased the most among women aged 20–29 years and stayed stable or decreased for women 35 and older. Paradoxically, the increase in the proportions of older mothers appeared to favor more stable rates over time in these countries.

Recent studies explored the relationship between preterm birth and disadvantaged socioeconomic circumstances [38–41]. Two studies found that social disadvantage was more strongly associated with very preterm than moderate preterm birth [42▪,43▪]. The 2010 WHO Multicountry study also found that less educated mothers had fewer provider-initiated preterm deliveries [44▪▪]. In northern England, although overall preterm birth rates stayed the same between 1960 and 2000, rates increased in the most deprived areas and decreased in less deprived areas resulting in widened social inequalities [45▪]. In Iceland, the 2008 economic crisis was associated with increases in the risk of low birth weight, but no change in preterm birth [46]. These studies illustrate the complexity of assessing the importance of social conditions in cross-national studies, both because of the variation across population sub-groups and the dependence on other contextual factors.

Migrant flows between European member states and from non-European countries have been increasing and migrant status has been identified as a risk factor for preterm birth [47▪,48,49▪]. In 2010, foreign born mothers represented between 0.0 (Poland) and 66.0% (Luxembourg) of childbearing women (Table 1). However, associations with preterm birth depend on preterm birth subtype (spontaneous vs. nonspontaneous), region of origin, reference groups used for comparison, reasons for migration (refugee, economic migrants), and length of residence [50,51▪▪,52]. A review by Urquia *et al.* [53] showed that adverse pregnancy outcomes in Europe were different depending on maternal country of origin. In another study, eastern European migrants had better perinatal health outcomes than United States born women even with later entry into prenatal care or less education, which may be explained by the healthy migrant effect [54]. However, in Sorbye *et al.*'s study of migrant women in Norway between 1999 and 2009, both spontaneous and nonspontaneous preterm birth rates were higher among immigrants than among Norwegian-born women. For migrants, provider-initiated preterm deliveries increased with increased length of residence, whereas spontaneous preterm deliveries remained unchanged [51▪▪].

Behavioral risk factors mediate the relationship between sociodemographic characteristics and preterm birth. A systematic review published in 2010 summarized the epidemiologic evidence on behavioral factors, including tobacco, alcohol, and illicit drug use, and physical, sexual, and occupational activity. The authors concluded that with the exception of tobacco, which was consistently but weakly associated with preterm birth, evidence for a causal role for other factors was slight [30]. A recent national French study added new results by showing that cannabis consumption increased spontaneous preterm birth risks; however, only 1.2% of women reported smoking during pregnancy [55].

Prenatal smoking rates vary across Europe, from 5 to 19% of women in the countries that could provide these data (Table 1). Smoking was found to explain differences in preterm birth rates between socioeconomic groups, about one-third of the variation in Finland from 1987 to 2010 [56▪]. However, in another international study, the effect was not as large across Europe [57]. A study from Belgium reported reductions in the risk of preterm birth subsequent to the introduction of smoking bans in 2007 and 2010 [58], raising the question of exposure to second-hand smoke [59,60▪]; however, other factors may have contributed to these observed effects.

Recent studies advanced our knowledge of the impact of maternal BMI on preterm birth, another maternal characteristic that varies in Europe (Table 1). Cnattingius *et al.* [31▪▪] found a dose–response relationship between maternal overweight and indicated preterm birth in a large population-based study from Sweden and also showed that obese women were at increased risk for extremely preterm delivery following premature rupture of membranes and spontaneous labor. This latter finding has been confirmed in other populations [61▪▪,62]. In a study that looked at more refined BMI categories including severe ($<16\,kg/m^2$), moderate ($16–16.99\,kg/m^2$), and mild thinness ($17–18.49\,kg/m^2$), Lynch *et al.* [61▪▪] showed that women at the lower extremes of BMI were at increased risk for both spontaneous preterm labor and medically indicated delivery.

Bloomfield [63], based on a review of epidemiological and experimental studies, posited an important role for poor maternal nutrition in the association between extreme BMIs and prematurity. Other studies also explored dietary risk factors for preterm birth, such as artificially sweetened drinks, which were responsible for increased preterm birth risk in two large cohort studies [64,65]. Further, probiotics, vitamin D, and vitamin C supplementation may reduce preterm birth risk by preventing genital infections, but more research is needed [66▪].

Recent studies examined the contribution of previous induced abortion to preterm birth rate [35,67▪▪]. The EuroPOP study had shown that

induced abortions were associated with preterm birth rates [68]. In Scotland, using data from the 1980s to 2000, this association was found to weaken over time and disappeared altogether by 2000, maybe because of changes in abortion methods [68]. However, a study from Finland showed no statistically significant difference in preterm birth by abortion method (4.0% in the medical group vs. 4.9% in the surgical group) [69]. In parts of Eastern Europe where there is a history of abortion being used as contraception, variations in the prevalence of induced abortion may impact on differences in preterm birth rates.

VARIATION OWING TO INDICATED PRETERM BIRTH

There is strong evidence that preterm birth rates in high-income countries are affected by obstetric practices related to indicated preterm births. Indicated singleton late preterm births have been identified as the main driver of North American preterm birth rates as opposed to changes in women's risk profiles [70–73]. Vanderweele *et al.* [74] showed that in the United States, although overall preterm births increased from 11.2 to 12.8% between 1989 and 2004, medically induced rates increased 94% from 3.4 to 6.6% and spontaneous rates declined by 21%, from 7.8 to 6.2%.

In Europe, Zeitlin *et al.* [9▪▪] showed that both spontaneous and induced preterm deliveries contributed to increasing preterm birth trends between 1996 and 2008; the contribution of each subgroup varied across countries, especially for singletons. In 2008, rates of nonspontaneous singleton preterm births ranged from 1.1 to 3.0%, whereas spontaneous onset preterm births ranged from 2.8 to 4.8%. For multiples, the rates of nonspontaneous preterm birth ranged from 12.0 to 34.4%, and spontaneous onset births from 15.1 to 38.2% [9▪▪]. In Scotland, for instance, between 1989 and 2004, nonspontaneous onset deliveries increased by almost 50% and spontaneous deliveries by 10% [75]. In other European countries, however, nonspontaneous onset preterm births have not increased over past decades.

Previous obstetric history and delivery mode are strong predictors of both spontaneous and indicated preterm delivery [32▪▪,76▪▪], but women's risk profiles can influence preterm birth subtypes in different ways. An Australian study, using population-based data from 1984 to 2006, showed that over time the population-attributable fraction associated with women's preexisting medical conditions and pregnancy complications increased, for both indicated and spontaneous preterm deliveries. The proportion of women with more than one medical condition increased from 4.9 to 19% in spontaneous preterm births and from 10.4 to 25.8% in medically indicated preterm deliveries [76▪▪].

Provider-initiated preterm births aim to improve the health of the child, and especially to reduce the risk of stillbirth; however, they are controversial, as evidence of the benefits to the child of early extraction are not always conclusive and countries have more or less interventionist policies. Variations in gestational age patterns of cesarean delivery rates in Europe were recently described; these suggest wide variations in clinical practice by gestational age and highlight areas where consensus on best practices is lacking [77▪]. Further research should analyze the extent to which increases in indicated preterm births have affected not only preterm birth rates but also perinatal mortality.

ENVIRONMENTAL FACTORS

Pregnant women are exposed to a myriad of environmental factors and this field of research is expanding [4]. Patel *et al.* [78] used United States national survey data from 2000 to 2006 and looked at 201 different environment factors (i.e., amount of chemical compound in tap water sources of participants) including the number one suspect in terms of adverse health outcomes, Bisphenol A (BPA), which proved to be associated with preterm birth. BPA may represent an important health threat because of its toxicity and high prevalence in everyday products.

Air pollution has also been linked in several recent studies to preterm birth. Air pollution exposures differ across Europe and vary over time [79▪▪]. For instance, urban population exposure to fine particulate matter has decreased between 2002 and 2011 in most countries except in central and eastern European countries where it increased dramatically [79▪▪]. Fine particulate matter may induce systemic inflammation, which could influence the duration of pregnancy [80▪]. Dadvand *et al.*'s [81▪] is the first study to report on the association between PPROM and PM2.5 and to report an increased risk of up to 50% in premature rupture of membranes associated with air pollution exposure. The negative impact of air pollution on gestational age was confirmed in Stieb *et al.*'s [82] 2012 meta-analysis, although there was a wide heterogeneity in study design and measures of exposure. More research on the physiological mechanisms through which air pollution influences gestational length is needed and clinical data are lacking from many observational studies.

Other environmental factors such as temperature [83,84▪▪,85,86] and UV light-induced vitamin D deficiency [87] have been explored, but it is unknown whether these could contribute to variations in preterm birth across countries.

INTEGRATED APPROACHES

Several recent studies tackled the larger question of how multiple population risk factors and medical practices explained preterm rate variations across countries or time. Zeitlin *et al.* [88▪▪] compared singleton preterm birth rates, based on obstetric estimates of gestational age, in France and the United States in 1995, 1998, and 2003; although many risk factors were different – in the United States, there were more teen pregnancies and women with insufficient prenatal care, but fewer smokers – adjustment for these factors did not reduce the constant excess risk of 70% in the United States (8.4% in the United States vs. 4.9% in France in 2003). Differences in rates could not be explained by obstetric interventions either: although preterm births associated with cesarean and induction were higher in absolute terms in the United States, spontaneous preterm birth rates were also elevated and the proportion of preterm births linked to these obstetrical interventions was the same. Garn *et al.* [89▪▪] compared maternal social and lifestyle characteristics, including stressful life events in Canada and the United States in 2005–2006 (preterm birth rates: 4.9 vs. 7.6%, respectively). Risk factors for preterm birth differed across countries and after adjustment, women in the United States still had a higher risk [89▪▪]. These results reinforce conclusions from a study which found that half of the increase in preterm birth rates from 1989 to 2004 (10.6–12.5%) in the United States remained unexplained after taking into account the contribution of maternal age, maternal race, maternal education, ART, multiple births, stillbirths averted, marital status, pregnancy intention, barriers to prenatal care initiation, as well as nonmedically indicated cesarean delivery and labor induction [7▪▪].

These studies illustrate the complexity of understanding the drivers of a country's preterm birth rate and pinpointing those that 'explain' the difference between countries. Multiple risk factors impact on preterm birth and studies in this review underscored the interdependence between them. Data on the whole range of key exposures are unlikely to be included in any one database and studies that combine databases face issues related to the comparability of data definitions [89▪▪]. Further, many risk factors interact with the type of preterm birth, that is spontaneous vs. indicated and differing approaches to indicated preterm births by country mean that common relationships may be obscured.

CONCLUSION

Among the multiple factors that emerged from this review of recent studies on preterm birth variations and trends within and between high-income countries, medical practices and policies related to subfertility treatments and indicated preterm deliveries had a clear impact on country-level preterm birth rates and trends. Understanding how some countries have maintained stable indicated preterm birth rates, whereas others have not – as well as the impact of these variations on child health – is an important research area. United States and Canadian studies showed that measurement of gestational age can have a large impact on the preterm birth rate estimate. Although this is unlikely to be a large contributor to European differences, we do not know whether gestational age determination differs across countries and it is important to rule out measurement artifacts. Finally, studies confirmed the role of many potentially modifiable population factors – BMI, smoking, and environmental exposures – in determining preterm birth risk. These factors likely interact and are associated with more general health and social policies that promote healthy childbearing. More knowledge about how these contribute to low and stable preterm birth risk would be enormously useful for shaping future policy.

Acknowledgements

This article drew on the work of the many people who contributed to the European Perinatal Health Report: The health and care of pregnant women and babies in Europe in 2010. They include statisticians, researchers, clinicians, administrators and others from each of the collaborating countries who compiled and submitted aggregated data for their countries to Euro-Peristat. They are too numerous to list here, but their names can found in Appendix A1 of the European Health Report at www.europeristat.com. The authors would like to thank them for their contributions.

Thank you to Dr Michael Kramer who provided valuable comments for this paper.

Financial support and sponsorship

The Euro-Peristat project was funded by a grant from the European Commission (2010 13 01). The funding agency was not involved in the study.

Conflicts of interest

There are no conflicts of interest.

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The underlying risk of preterm birth was generally higher in the United States. Between-country comparisons can help identify potential modifiable risk factors contributing to preterm birth.

Updated review: State of the art including studies from 2014-2017

In our review, we identified the most likely determinants of PTB variations across countries. These include medical practices and policies related to ART and indicated delivery, GA measurement methods, and modifiable risk factors such as BMI, smoking, and environmental exposures. Here, we now highlight important findings from studies between 2014 and 2017 that further add to our understanding of PTB risk factors at the population level.

New evidence confirms the impact of ART, multiple births, and socio-demographic characteristics. Kushnir et al. showed an increasing use of subfertility treatments globally (i.e. in Australia/New Zealand, Japan, the US, Canada, European countries, and Latin America between 2004 and 2013). Their study also documented high rates of preterm birth ranging between 9.0 to 16.6% for ART-singletons, 53.9 to 67.3% for ART-twins, and 91.4 to 100% for ART-triplets and higher order multiples (58). As for sociodemographic risk factors, persistently higher rates of PTB are found in some migrant groups such as women from Sub-Saharan Africa, but the explanations for the association between ethnicity and PTB risk are still unclear (106, 112). A recent study by Sorbye et al. suggests that differences may reflect lasting SES disadvantage and not genetic mechanisms per se (106). In Europe, low maternal education was associated with an excess risk of preterm birth with marked inequalities in the Netherlands, the UK, Sweden and Spain (92). The most recent US findings relate national income inequality to PTB time trends (116).

Recent studies also add to the literature on the importance of behavioral risk factors such as physical activity, dietary intake, and smoking. A recent systematic review showed that higher leisure-time activity is associated with reduced risk of preterm birth (9). New studies challenge any protective effect of folic acid (73, 93) but suggest a role for vitamin B12 intake (89). More generally a “prudent” diet high in fruits, vegetables, and whole grain cereals, is associated with

reduced PTB risk compared to a "Western" diet composed of processed foods, or a "traditional" Nordic diet (i.e. potatoes and fish) (32). In the UK, smoking and a poor diet during pregnancy were strongly associated with increased risk of preterm birth and very preterm birth in particular(104), while women who stopped smoking before the third trimester were found to display similar preterm birth rates as those of nonsmokers in a subsequent pregnancy (115).

Between 2014 and 2017, there were also important and original data on environmental exposures and PTB risk. Whereas studies thus far looked at single teratogenic agents (ie. BPA) or domain-specific exposures (i.e. air pollution), Rapazzo et al. demonstrated the value of a large scale composite environment exposure metric (Environmental Quality Index, EQI), and a contextual approach to prevention. The study looked at the cumulative effect of air, water, land, sociodemographic and built environment characteristics on PTB risk in the US from 2000-2005. Although an overall association between EQI and PTB risk was not found, there was a strong association between preterm birth and poor air quality with differences across urban and rural stratum (86). There is also new data on the risk of PTB and increases in atmospheric pressure from a pooled analysis of 13 birth cohorts in 11 European countries (44). Integrated risk factor approaches may provide important evidence for PTB prevention, especially in the design of large-scale policy interventions, or health impact assessments (i.e. in urban policy planning).

Finally, other studies provided evidence that contrasts with previous reports; these are related to the impact of obstetrical interventions and maternal age on PTB risk. In our review, we found that mean levels of obstetrical interventions most likely influenced global PTB variations. A recent study also showed that cesarean section in the first pregnancy is a significant risk factor for preterm birth in the next pregnancy (118). However, an international study by Richards et al. showed that decreases in provider-initiated births were associated with decreases in early term births in the US, but there was no association with early delivery (i.e. late PTB or early term birth) in the Nordic countries (87). These findings should be interpreted

with caution. Besides Norway where PTB decreased, other Nordic countries had rather low and stable PTB rates over the study period (2006-2014) which might explain the lack of association. As for maternal age, it may not be as strong of a risk factor for preterm delivery as previously reported. In the US between 2007 and 2014, increases in births to mothers aged 30 years and over, had no effect on PTB (35). In France, advanced maternal age was a risk factor for preterm birth in 1995 but not in 2010 (84). In the UK, preterm delivery and other complications in mothers 48 and over were mostly explained by multiple pregnancy and subfertifity treatments (39). This evidence raises questions about potential interactions between individual and clinical risk factors, and changes in baseline risk in the general population.

In conclusion, new studies provide promising research areas for prevention, confirming that socio-economic disparities (80), behavioral risk factors and environmental exposures could be further invested in by prevention. However, our review also highlights the complexity of pin-pointing one specific reason for rate differences across countries, as there are multiple population determinants which could have small to moderate impact on the preterm birth risk. More research including a range of exposures as well as sufficient sample sizes is needed on population determinants of PTB. Moreover, there have been few cross-country studies on PTB risk factors, and the ones that have been published are based on a limited number of countries. Zeitlin et al. compared France to the US (121) , Garn et al. compared Canada vs. the US (43), and Richards et al. compared the Nordic countries (i.e. Sweden, Norway, Denmark, and Finland) vs. the US (87). While these studies compared countries with similar levels of PTB (i.e. Canada and the US) and very different PTB rates (ie. Nordic countries and the US), given reported differences in the measurement of GA and registration practices for births and deaths across countries, it is unclear which methods and criteria should be used in international comparisons of PTB risk factors and rates. In sum, a clear description of the underlying mechanisms of shifts in the preterm birth rate and trends have not been identified, and we do

not know how population determinants may accrue and interact with maternal risk profiles or countries' baseline rates.

Chapter 3: Methods

Data from Europe were collected by the Euro-Peristat project. Data from the US, Canada and Japan were provided by PREBIC using the Euro-Peristat data collection protocol, and data from Australia were from the NSW Data collection on births. We also used individual-level data from the 2010 French National Perinatal Survey, a representative sample of births in France. In total, these international networks and collaborations allowed us to collect official statistics on births from 34 countries and regions in 1996, 2000, 2004, 2008 and 2010.

1. Data sources

Aggregate data from European countries: The Euro-Peristat project

The Euro-Peristat project was set up in 1999 as part of the EU's Health Monitoring Programme to specifically address the surveillance of over 5 million pregnant women in Europe and their babies. The Euro-Peristat project is a well-known reference in the field and it has been recognized as one of the most successful projects funded by the EU Health Programme. The project is coordinated in France at INSERM the French National Institute of Health and Medical Research, by the UMR1153-EPOPé research team. It has official representation from thirty-one European countries: 28 EU member states and Iceland, Norway, and Switzerland. In each country, a Scientific Committee (SC) member is responsible for compiling the Euro-Peristat indicators from their national health information systems. The SC member collaborates with one or more other data providers. The full list of contributing members is available in Appendix C.

The Euro-Peristat indicators were defined in 2000 based on a review of the literature, and a DELPHI consensus process among European perinatal health experts. The project agreed on a set of 10 Core indicators essential for monitoring perinatal health, and 20 Recommended

indicators which provide a more complete picture across countries. The indicators are grouped into four themes: (i) maternal health, (ii) fetal, neonatal and child health, (iii) health services and use, (iv) population characteristics and risk factors. The indicators are compiled using aggregate data from population-based routine sources. Routine data sources are defined as those that regularly collect and report data and can include repeated surveys. The indicators are collected on all live and stillbirths starting at 22 weeks of GA for each completed week of gestation. If gestational age is missing, only births 500g or more are included.

Perinatal data essentially come from vital statistics, civil registers and medical birth registers in European countries and from nationally representative surveys of births. Supplementary information on the characteristics (i.e. data quality, management, coverage) of the data sources used to collect the indicators are also requested (45); these are provided in Appendix A. If countries cannot provide national data, population-based data from geographically defined regions are accepted.

The specificities of the Euro-Peristat project are (1) use of a common data collection protocol which includes data quality checks and internal and external validation. (2) feasibility and availability of the indicators in routine data sources for better cross-country comparability (3) data collection using sub-groups for more in-depth analyses of indicators (4) creation of a network of specialists who actively partake in data collection and interpretation. (5) capacity building for cross-country data sharing and analyses using the Euro-Peristat indicators.

The project published two European Perinatal Health Reports in 2008 and 2013. These publications are based on the full list of indicators (core and recommended) and provide a comprehensive overview of the health status and care of pregnant women and babies in Europe in 2004 and 2010. The project also conducts ad-hoc analyses of country data for scientific articles. Euro-Peristat data are used by many key maternal and child health stakeholders:

clinicians (obstetricians, neonatologists, midwives, and neonatal nurses), researchers, policy makers in health ministries, protection offices, insurance and quality assurance agencies, as well as perinatal health organisation representing pregnant women and their families.

Aggregate data from the US, Canada and Japan: The PREBIC project

The collaboration between Euro-Peristat and PREBIC started in 2012 and focused on a shared methodology for preterm birth analyses using international data. To this aim, the Euro-Peristat data collection protocol was expanded to countries participating in PREBIC: the US, Canada and Japan. The PREBIC Epidemiology Working Group is a multi-disciplinary network of scientific experts focused on the prevention of preterm birth through basic, epidemiologic, and applied clinical research. The project was initiated with support from the World Health Organization and the March of Dimes foundation. For this thesis, national experts provided data on the gestational age distribution of births in their country and country-specific input regarding the interpretation of the analyses.

Aggregate data from Australia: New South Wales

Aggregate data from New South Wales, which represents a third of births in Australia were obtained from Dr. Natasha Nassar who had access to the NSW Births database at the Menzies Center of Health and Policy. These were also collected using the Euro-Peristat protocol.

Individual-level data from France: French National Perinatal Survey 2010

In addition to data provided to the Euro-Peristat project in aggregate form, individual level data from the French Perinatal Survey in 2010 (*Enquête Nationale Périnatale 2010*) were used. The French Perinatal Surveys are population-based representative surveys which are conducted

over the course of one week in public and private maternity units in Metropolitan France. Data collection is coordinated by the INSERM UMR1153-EPOPé research team.

2. Data and definitions

Aggregate data on the gestational age distribution, defined as the number of births at each completed week of gestation, were collected using a common protocol on births in 2010 (26 EU Member States and Norway, Switzerland and Iceland), 2004 (25 EU Member States and Norway) and 2000 (15 EU Member States). Aggregate data were stratified by multiplicity (singleton/multiples) and vital status (stillbirth/live birth). In a separate study on preterm birth, Euro-Peristat collected information on the number of singleton live births by completed week of gestation by method of delivery and mode of onset in 17 countries/regions for the years 1996, 2000, 2004 and 2008 (124).

Aggregate data items included in these 2 databases were collected from other participating countries using the Euro-Peristat data collection protocol. In all studies, gestational age was requested using the best obstetric estimate. When gestational age was missing, we asked countries to include births if birth weight was 500 grams or more. If countries could not provide data using these criteria, they were asked to provide available data using their own inclusion criteria, and to specify their inclusion thresholds for births and deaths. We also asked for separate data on late terminations of pregnancy (TOP), when these were included in the data sources and could be differentiated from spontaneous stillbirths. Data were available on mode of delivery and mode of onset of labour. Indicated deliveries were defined as those that were provider-initiated including: inductions, prelabor and emergency cesarean sections, based on national classifications.

3. Study population

Population-based data on the gestational age distribution were available from 34 countries in North America, Europe, Japan and Australia in at least one time point for which data collection was undertaken (1996, 2000, 2004, 2008 and 2010). However, not all countries could provide all data points and these differences in data availability are accounted for in our analyses as detailed in the specific chapters. Also, some countries only had data available for selected regions. Data for Belgium (BE) came from Brussels, Wallonia and Flanders; data from the United Kingdom were provided separately by the UK's constituent countries: England and Wales combined, Northern Ireland, and Scotland. In 1996-2000, Germany provided data from three Länder: Hesse, Lower Saxony and Bavaria. In 2008, data from Canada included all provinces and territories except the province of Ontario; in 2010, data from all provinces were included except for Québec. Some countries had different years of data available. Data from Cyprus were from 2007. In Malta and Sweden data were provided for 2009. In France, data were from 1995, 1998, 2003 and 2010; in Canada and UK: England and Wales, data were from 2005 instead of 2004.

4. Analysis strategy

Data from the Euro-Peristat project were aggregated at the country-level therefore we conducted ecological analyses. Ecological analyses are a powerful tool to test hypotheses about the broader determinants of disease when there are many observations, and these are clustered into groups. These analyses rely on assessing associations between exposures and outcomes measured at the population level. We used both Spearman's non-parametric and Pearson's parametric tests.

In Chapter 4, our objective was to assess the robustness of preterm birth country rankings using data from 32 countries in 2008, and we used Spearman's rank test to relate VPT

birth rates based on all births starting at 22 weeks to rates based on other reporting criteria (i.e. all births starting at 24 weeks GA). *Spearman's rho* ρ is the correlation coefficient between the ranked variables and therefore is less sensitive to outlying values; it is generally considered a more conservative estimate than *Pearson's r* and recommended for use in ecological studies.

In Chapter 5, our objective was to relate changes in preterm birth rates to broader changes in other GA subgroups and we used Pearson's test to examine possible associations. We conducted a time series analysis of preterm birth rates (using data on multiple time points within each country between 1996 and 2010), therefore we selected the Pearson's test because it was possible, using Lorenz's formulae to compute a marginal association measure that remains valid under the clustered data framework (i.e. PTB rates are clustered by country over time). Whereas both Pearson's and Spearman's test assume the observations are independent from one another; the adjusted Pearson's estimate takes into account the variance within and across clusters, and their size (64). For paired data (X, Y) collected on a set of M clusters, let (X_{ij}, Y_{ij}) be the jth observation (ie. PTB rate in each study year) for cluster I (i.e. Country), where $1 \leq i \leq M$ refers to the number of countries and $1 \leq j \leq n_i$ refers to the number of observations within countries.

The adjusted-Pearson's estimator is defined by the formula:

$$\hat{\rho}_{\mathrm{m}} = \frac{\bar{W}_3 - \bar{W}_1 \bar{W}_2}{\sqrt{\left(\bar{W}_4 - \bar{W}_1^2\right)\left(\bar{W}_5 - \bar{W}_2^2\right)}}.$$

where,

$$W_{1i} = n_i^{-1} \sum_{j=1}^{n_i} X_{ij},\ W_{2i} = n_i^{-1} \sum_{j=1}^{n_i} Y_{ij},\ W_{3i} = n_i^{-1} \sum_{j=1}^{n_i} X_{ij} Y_{ij},\ W_{4i} = n_i^{-1} \sum_{j=1}^{n_i} X_{ij}^2,\ \text{and}\ W_{5i} = n_i^{-1} \sum_{j=1}^{n_i} Y_{ij}^2$$

and,

$$\bar{W}_k = M^{-1} \sum_{i=1}^{M} W_{ki}$$

An important drawback of ecological analyses is the loss of information and potential for confounding. The risk of ecological fallacy is characterized by wrongly inferring results for the individual based on outcomes at the aggregated level. These limitations are discussed in each of the analyses.

In Chapter 6, we explored population risk factors for early delivery using individual data from the French National Perinatal Survey. We conducted multinomial logistic regression analyses to look at the impact of maternal and pregnancy characteristics on risks of earlier delivery using two GA subgroup categories: preterm births and early term births, in comparison to a reference group of births at 39 weeks or over.

For the ecological studies using Euro-Peristat data, all data used for the analyses are provided in Appendix B and data were published with the papers. Data were analysed using STATA 13.0 software (StataCorp LP, College Station, TX, USA), while adjusted analyses were conducted using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria). More details on methods are provided in the individual chapters.

Chapter 4: Are valid international comparisons possible using routine GA data?

Targets to inform PTB prevention should be based on accurate estimates of the preterm birth burden. However, we saw in Chapter 1 that there can be measurement artefacts including differences in recording practices for births and deaths across countries. The GA criteria for inclusion of infants in perinatal statistics vary from country to country which raises questions about the validity of PTB rates compiled from routine systems (45, 72). On the other hand, comprehensive monitoring of the most vulnerable children, especially those born very preterm, is required to evaluate the uptake of prevention policies for the highest risk infants.

In this chapter, we address concerns about the comparability of GA at the earliest gestational ages. We developed a methodology for valid comparisons of preterm birth rates using routine data sources. We had data on 9,376,252 singleton births in 32 countries in 2010. We used two indicators: percent of stillbirths and periviable births (22-23 weeks) among very preterm births to identify countries with registration biases that might impact on VPT rates and rankings. There were wide variations in rates from 5.7 to 15.7 per 1000 total births and 4.0 to 11.9 per 1000 live births. Percent of stillbirths also varied greatly by gestational age: between 20 and 100% for births 22-23 weeks across countries, and were related to registration practices. Some countries which could not distinguish terminations from spontaneous stillbirths in their vital statistics were penalized in their rankings; otherwise these were robust to underreporting. Our methodology allowed us to identify true and large differences in VPT rates across countries.

Our results have been published under the following citation:

Delnord M, Hindori-Mohangoo AD, Smith LK, et al. Variations in very preterm birth rates in 30 high-income countries: are valid international comparisons possible using routine data? BJOG. 2017 Apr; 124(5):785-794. doi: 10.1111/1471-0528.14273. Epub 2016 Sep 10.

We also provide our response to an exchange with:

Dr. Boris Filipović-Grić & Urelija Rodin

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Our letter was published under the following citation:

Delnord M, Zeitlin J. Authors' reply re: Variations in very preterm birth rates in 30 high-income countries: are valid international comparisons possible using routine data? BJOG. 2017 Sep;124(10):1624-1625. doi: 10.1111/1471-0528.14642. Epub 2017 Jun 27.

BJOG An International Journal of Obstetrics and Gynaecology

DOI: 10.1111/1471-0528.14273
www.bjog.org

Variations in very preterm birth rates in 30 high-income countries: are valid international comparisons possible using routine data?

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Accepted 18 July 2016. Published Online 9 September 2016.

Objective Concerns about differences in registration practices across countries have limited the use of routine data for international very preterm birth (VPT) rate comparisons.

Design Population-based study.

Setting Twenty-seven European countries, the United States, Canada and Japan in 2010.

Population A total of 9 376 252 singleton births.

Method We requested aggregated gestational age data on live births, stillbirths and terminations of pregnancy (TOP) before 32 weeks of gestation, and information on registration practices for these births. We compared VPT rates and assessed the impact of births at 22–23 weeks of gestation, and different criteria for inclusion of stillbirths and TOP on country rates and rankings.

Main outcome measures Singleton very preterm birth rate, defined as singleton stillbirths and live births before 32 completed weeks of gestation per 1000 total births, excluding TOP if identifiable in the data source.

Results Rates varied from 5.7 to 15.7 per 1000 total births and 4.0 to 11.9 per 1000 live births. Country registration practices were related to percentage of births at 22–23 weeks of gestation (between 1% and 23% of very preterm births) and stillbirths (between 6% and 40% of very preterm births). After excluding births at 22–23 weeks, rate variations remained high and with a few exceptions, country rankings were unchanged.

Conclusions International comparisons of very preterm birth rates using routine data should exclude births at 22–23 weeks of gestation and terminations of pregnancy. The persistent large rate variations after these exclusions warrant continued surveillance of VPT rates at 24 weeks and over in high-income countries.

Keywords Euro-Peristat, international comparisons, preterm birth, stillbirths, very preterm.

Tweetable abstract International comparisons of VPT rates should exclude births at 22–23 weeks of gestation and terminations of pregnancy.

Please cite this paper as: Delnord M, Hindori-Mohangoo AD, Smith LK, Szamotulska K, Richards JL, Deb-Rinker P, Rouleau J, Velebil P, Zile I, Sakkeus L, Gissler M, Morisaki N, Dolan SM, Kramer MR, Kramer MS, Zeitlin J. Variations in very preterm birth rates in 30 high-income countries: are valid international comparisons possible using routine data?. BJOG 2016; DOI: 10.1111/1471-0528.14273.

[†]See Appendix for the members of the Euro-Peristat Scientific Committee.

Introduction

Preterm birth, defined as a birth before 37 completed weeks of gestation, is a leading cause of neonatal and infant mortality globally, representing about 75% of all neonatal deaths and 60% of all infant deaths.[1,2] Infants born very preterm (before 32 completed weeks of gestation) face the highest risks of neonatal mortality and morbidity, as well as long-term neurodevelopmental impairment.[3–6] Recent studies showed wide variations in total preterm births among countries with comparable levels of development and healthcare systems, raising questions about the population and health system factors that influence preterm birth.[1,7–9] However, less is known about international variation in very preterm birth, which represents the most vulnerable infants.

There are concerns about using routine statistics for international comparisons at very early gestational ages because of differences in recording practices across countries;[10–15] especially regarding regulations for stillbirths and late terminations of pregnancy (TOP).[14,15] Further, differences in views on viability can influence whether births with signs of life that occur at 22 and 23 weeks of gestation are actually registered as live births or stillbirths.[16] Differences in recording practices have been shown to have a strong impact on international comparisons of perinatal mortality.[10–15] Hence, although the World Health Organization defines the perinatal period as starting at 22 completed weeks (154 days) of gestation, they recommend restricting international comparisons of perinatal mortality to third-trimester births, using a 1000-g lower threshold.[17] Others have used 28 weeks of gestation as a cut-off for comparative studies.[14] These cut-offs are not useful for comparisons of very preterm (VPT) rates because many births occur before 28 weeks and/or with birthweights <1000 g, and the majority of these infants now survive in high-income countries.[4]

Given the impact of very preterm births on the overall perinatal mortality rate, the high costs of care for these infants,[6,18,19] and their vulnerability to long-term neurodevelopmental impairments, producing comparable and regularly reported statistics on this population is an important objective. Our study aimed to assess the feasibility of using routine statistics to make valid international comparisons of VPT rates. We used routine population-based data in 2010 in 27 European countries, the USA, Canada and Japan to describe very preterm birth rates and investigate the extent to which births at very early gestations (22–23 weeks), stillbirths and TOP affect rate variations.

Methods

Data

This study is part of an international collaboration between the Euro-Peristat network and the Preterm Birth International Collaborative (PREBIC) Epidemiology Working Group. Euro-Peristat is a European Union-funded network of clinicians, statisticians and researchers that aims to monitor perinatal health in Europe based on a recommended set of 30 perinatal health indicators.[20] These indicators are compiled from population-based routine data sources; routine sources are defined as those that regularly collect and report data and can include repeated surveys. European data in this study were originally collected for the *European Perinatal Health Report: the Health and care of pregnant women and babies in 2010*.[1] Data from the USA, Canada and Japan were provided specifically for this study by members of the PREBIC Epidemiology Working group. PREBIC is a multi-disciplinary network of scientific experts focused on the prevention of preterm birth through basic, epidemiologic, and applied clinical research.

We requested aggregate national-level data on the number of live births and fetal deaths at each completed week of gestation by plurality (singleton or multiple) starting at 22 weeks in 2010. We also asked for separate data on TOP, when these were included in the data sources and could be differentiated from spontaneous stillbirths. When gestational age was missing, we asked countries to include births if birthweight was ≥500 g. The 22 weeks of gestation threshold is recommended by Euro-Peristat for the collection of all data on births in Europe.[20] If countries could not provide data using these criteria, they were asked to provide available data using their own inclusion criteria, and to specify their inclusion thresholds for live births and stillbirths.

Data came from vital statistics, civil registers and medical birth registers in most countries and from nationally representative surveys of births in Cyprus and in France.[1] If countries could not provide national data, population-based data from geographically defined regions were accepted. Data for Belgium (BE) came from the regions of Brussels, Wallonia and Flanders; data from the UK were provided separately by the UK's constituent countries: England and Wales combined, Northern Ireland and Scotland. Data from Cyprus were from 2007 and data from Canada were from 2008. Data from Canada included all provinces and territories except the province of Ontario. Euro-Peristat also collects information on data quality, management, and data collection procedures.[15] The sources of data used for each of the countries and their coverage are provided in the Supplementary material (Table S1).

Outcome

Our principal outcome was the singleton very preterm birth rate, defined as all singleton stillbirths and live births before 32 completed weeks of gestation per 1000 total births, excluding TOP if identifiable in the data source. We also computed the singleton live VPT rate (number of singleton live very preterm births per 1000 live births). We

limited our comparison to singleton pregnancies, because preterm birth rates are much higher for multiple pregnancies and multiple pregnancy rates differ widely among countries.[9,21]

In the European countries, Canada and Japan, gestational age was based on the best obstetric estimate. This estimate can be derived from ultrasound, and other prenatal assessments of gestational length (i.e. last menstrual period, fundal height). In Canada, postnatal assessments may sometimes be used if ultrasound data are missing. In the USA, the obstetric estimate of gestational age was used in the 35 states that had adopted the 2003 birth certificate revision; however, 15 states used the 1989 revision, which relies on the clinical estimate of gestational age, and is based on postnatal assessment in addition to ultrasound and prenatal assessments.[22,23] In the USA, birth and death data are linked from separate data sources. Out of the 35 states that had adopted the 2003 revision for live birth certification, only 25 had adopted the 2003 revision for fetal death certification, whereas other states reported only the 1989 revision.[24] In our study, less than 1% of gestational age data were missing, except in Spain, where 14% were missing.

Analysis strategy

For this study, we identified countries where differences in registration practices may contribute to variability in rates. First, we assessed whether the data provided by each country met our inclusion criteria: births and deaths starting at 22 weeks of gestation for each completed week of gestation, excluding terminations. We identified countries using different birthweight or gestational age criteria, as well as countries that included TOP in their vital statistics but could not distinguish them from spontaneous births. Next, we calculated the rates of singleton very preterm births for all births <32 weeks of gestation using a lower threshold of 22 weeks of gestation or national definitions. We then evaluated the influence of periviable births (defined as births at 22–23 weeks of gestation) and stillbirths on country rates and rankings by comparing VPT rates with and without these births. We also calculated percentages of periviable births, and stillbirths (for births ≥22 weeks of gestation versus ≥24 weeks of gestation), among very preterm births, and percent of stillbirths by gestational age subgroups: at 22–23 weeks, 24–27 weeks and 28–31 weeks of gestation. We studied the association between rates for total and live births overall and by gestational age subgroups using Spearman's rank test. Last, we investigated the potential impact of under-reporting of stillbirths, after exclusion of births at 22–23 weeks, by simulating an extreme situation where a third of stillbirths 24–27 weeks of gestation were not reported in countries with higher registration thresholds. Data were analysed using STATA 13.0 software (StataCorp LP, College Station, TX, USA).

Results

Thirty countries provided data on 9 376 252 singleton births, of which 9 339 331 were live births and 36 921 were stillbirths. All countries could provide data on singleton live births starting at 22 weeks of gestation, but several countries record stillbirths only starting at 24 weeks of gestation or use a 500-g birthweight threshold, as detailed in Table 1. Most countries could also provide data without TOP, either because they are not included in birth registers or because they can be distinguished from other deaths. However, Belgium, Cyprus, the Czech Republic, Iceland, Luxembourg, the Netherlands, Slovenia, Spain, UK: England and Wales, and UK: Northern Ireland could not exclude TOP from their statistics.

The median singleton VPT rate among participating countries was 9.5 per 1000 births. Countries with the lowest rates, that is, below the 25th centile (Q1 = 8.5‰) included Iceland, Finland, Japan, Sweden, Italy, Slovakia, Norway and Malta. Countries with the highest rates, above the 75th centile (Q3 = 10.8‰) included Germany, UK: England and Wales, UK: Scotland, the Netherlands, Romania, Latvia, the USA and BE: Brussels (Table 1).

Figure 1 illustrates the variations in births (live births and stillbirths) at 22–23 weeks of gestation as a proportion of all very preterm singleton births; the associated registration practices for births and deaths in each country are also shown. The unweighted mean for the 30 countries (9.6%) is presented here with 95% upper and lower confidence limits. The percentage of periviable births among very preterm births varied between 0.7% and 23.4% across countries, and 18 of 30 countries/regions displayed proportions outside the 95% confidence limits. Countries with a 24 weeks of gestation threshold for registration of stillbirths, voluntary reporting of stillbirths at certain gestational ages, or those using a 500 g threshold for stillbirth reporting, had lower proportions of these very early births: Romania (0.7%), Portugal (1.5%), Spain (3.5%), Italy (4.3%), UK: England and Wales (5.0%), Ireland (6.3%), UK: Scotland (6.9%), and Germany (8.3%). However other countries with a 22-week threshold also had low rates, notably, Slovakia (2.2%), and Latvia (4.0%). Countries that were unable to remove TOP had higher proportions of births at 22–23 weeks of gestation, including BE: Brussels (15.7%), the Czech Republic (23.3%) and the Netherlands (23.4%). Nonetheless, others where data included only spontaneous stillbirths also had high rates such as Japan (11.5%), Denmark (12.4%), the USA (13.7%), Switzerland (14.0%) and Canada (14.4%).

Table 1. Singleton very preterm birth rates in 30 countries in 2010 and associated reporting criteria for births and deaths

Reporting criteria for stillbirths**	Country	Total births, *n*	Very preterm births, *n*	Rate per 1000 total births*	95% CI
≥22 weeks, no TOP	Canada***	229 700	2185	9.5	9.1–9.9
	Denmark	60 896	556	9.1	8.4–9.9
	Estonia	15 412	154	10.0	8.4–11.6
	Finland	59 484	397	6.7	6.0–7.3
	France	14 402	138	9.6	8.0–11.2
	Japan	1 083 473	8236	7.6	7.4–7.8
	Latvia	18 764	225	12.0	10.4–13.6
	Lithuania	30 167	272	9.0	7.9–10.1
	Malta	3872	32	8.3	5.4–11.1
	Norway	60 836	502	8.3	7.5–9.0
	Slovakia	54 204	447	8.2	7.5–9.0
	Sweden	111 705	860	7.7	7.2–8.2
	Switzerland	77 266	656	8.5	7.8–9.1
	United States	3 873 943	54 779	14.1	14.0–14.3
≥22 weeks, with TOP	BE: Brussels	23 933	376	15.7	14.1–17.3
	BE: Flanders	67 330	625	9.3	8.6–10.0
	BE: Wallonia	37 133	333	9.0	8.0–9.9
	Cyprus***	8133	83	10.2	8–12.4
	Czech Republic	112 116	1140	10.2	9.6–10.8
	Iceland	4765	27	5.7	3.5–7.8
	Luxembourg	6321	64	10.1	7.6–12.6
	Netherlands	172 707	1978	11.5	10.9–12.0
≥24 weeks, no TOP	Romania	209 120	2397	11.5	11.0–11.9
	Portugal	98 690	870	8.8	8.2–9.4
	Sweden	111 705	860	7.7	7.2–8.2
	UK: Scotland****	55 654	619	11.1	10.2–12.0
≥24 weeks, with TOP	UK: England and Wales**	699 494	7710	11.0	10.8–11.3
	UK: Northern Ireland	24 900	245	9.8	8.6–11.1
180 days, no TOP	Italy****	529 182	4254	8.0	7.8–8.3
180 days, with TOP	Spain****	444 217	4438	10.0	9.7–10.3
+500 g or ≥24 weeks, no TOP	Ireland	73 041	635	8.7	8.0–9.4
+500 g, no TOP	Austria	76 226	820	10.8	10.0–11.5
	Germany	613 796	6696	10.9	10.6–11.2
	Poland	403 781	3816	9.5	9.2–9.8
+500 g, with TOP	Slovenia	21 589	228	10.6	9.2–11.9
Total births (*n*)		9 376 252	106 793		
Median rate (‰)				9.5	8.9–10.2
Interquartile range				8.5–10.8	
Range				5.7–15.7	

*Using lower threshold of 22 weeks of gestation for births and deaths without TOP, or national definitions as specified.
**All countries could provide data on live births starting at 22 weeks of gestation.
***Data from Cyprus are from 2007, data from Canada are from 2008.
****Incomplete registration for stillbirths before 180 days in Spain and Italy, and before 24+ weeks in UK: Scotland.

Stillbirths constituted an average 20.6% of all very preterm births for the 30 countries, with a range between 5.9% and 39.9%, as shown in Figure 2A. Some of the countries with the lowest rates had other inclusion criteria, and those with the highest could not exclude terminations. There was substantially less variation around the mean after excluding births at 22–23 weeks of gestation, although percentages ranged from 6.0% to 29.6% even in countries with similar registration criteria (Figure 2B). For example, Estonia (11.3%), USA (11.6%), Norway (12.1%), Denmark (12.7%), Canada (14.7%), Sweden (14.8%), Switzerland (14.9%) and Finland (15.4%) had proportions below the average in 30 countries, whereas Lithuania (17.5%), Japan (17.7%), Latvia (19.0%), Malta (21.4%), France (29.6%) and Luxembourg (29.6%) displayed high percentages.

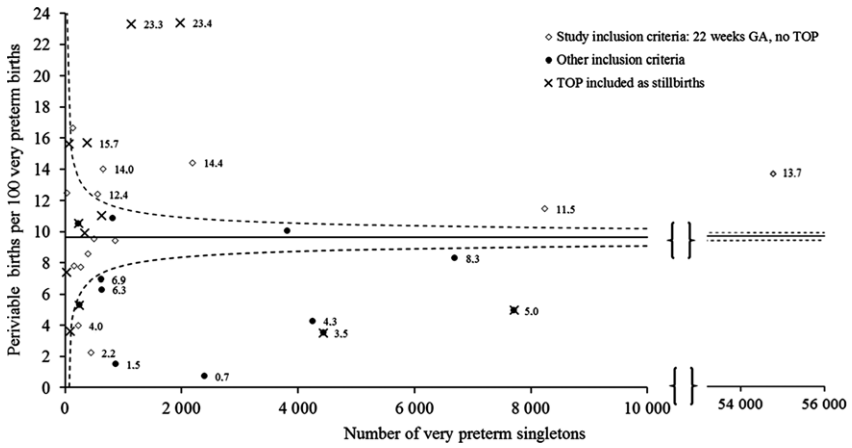

Figure 1. Births at 22 and 23 weeks as a percentage of singleton very preterm births in 30 countries in 2010 according to registration practices for births and deaths.

The median percentage of stillbirths was 58.8% at 22–23 weeks of gestation, 24.8% at 24–27 weeks and 10.6% at 28–31 weeks. Variation was particularly high at 22–23 weeks ranging from 10.4% in Italy to 100% in Iceland and Cyprus; Iceland and France stood out as outliers based on the overall distribution of stillbirths at 28–31 weeks of gestation (Figure S1). Median rates of births at 22–23 weeks were 0.9 per 1000 for all births versus 0.3 per 1000 for live births; at 24–27 weeks of gestation, 2.8 per 1000 for all births versus 2.1 per 1000 for live births and at 28–31 weeks of gestation, 5.5 per 1000 for all births versus 4.9 per 1000 for live births (Figure S2).

In general, countries with high rates in one gestational age category were more likely to have higher rates in the others, with the exception of the 22–23-week category. For live birth rates at 22–23 weeks of gestation, and 24–27 weeks of gestation, the rank correlation coefficient was 0.37 ($P = 0.02$), and with live births at 28–31 weeks it was 0.1 ($P = 0.77$). The correlation was strongest (0.53) for live birth rates at 24–27 weeks of gestation and 28–31 weeks of gestation ($P < 0.01$). The correlation between total birth and live birth rates was 0.43 ($P = 0.01$) at 22–23 weeks of gestation, 0.82 ($P < 0.01$) at 24–27 weeks of gestation, and 0.94 ($P < 0.01$) for births at 28–31 weeks of gestation.

In Table 2, we compare countries' very preterm birth rates and rankings using different gestational age criteria (22+ versus 24+ weeks of gestation) for all births and live births. Rates of all births from 24 to 31 weeks ranged from lower values of 5 to upper values of 13 per 1000, whereas for live births the range was from 4 to 11 per 1000. In general, countries with high rates for all births remained high when births at 22–23 weeks of gestation and stillbirths were excluded, and those with lower rates remained low. Rates were strongly correlated: the correlation coefficient for rates based on total very preterm births 22+ weeks of gestation and live births 24+ weeks was 0.78 ($P < 0.01$, and for live and total births at 24–31 weeks of gestation, the correlation coefficient was 0.92 ($P < 0.01$). Countries in the higher and lower quartiles of the distribution regardless of the definition remained the same, with a few exceptions (Italy is ranked lower while France had a better ranking when stillbirths were removed). Furthermore, our sensitivity analysis based on an extreme situation (one-third under-reporting of stillbirths at 24–27 weeks of gestation) in countries that do not record stillbirths starting at 22 weeks, showed that differences in rates and rankings were robust to potential residual under-reporting (Table S2).

Discussion

Main findings

Very preterm birth rates varied widely across Europe, North America and Japan. Our analyses by gestational age subgroups and vital status suggest that rates are influenced by differences in lower gestational age and birthweight thresholds for recording births and deaths, and the capacity for identifying TOP. These differences have a strong impact on the reporting of births at 22 and 23 weeks of gestation. However, after excluding these births, we noted large variability between countries; rates and rankings were robust to the potential effects of stillbirth under-reporting at 24–27 weeks of gestation, suggesting true differences beyond measurement or registration artefacts. Given the impact of very preterm births on newborn and child health, routine data on these births should be monitored to understand variation across countries and over time. Two indicators: births at 22–23 weeks and stillbirths as percentages of all very preterm births, made it possible to flag countries where recording practices may require further assessment.

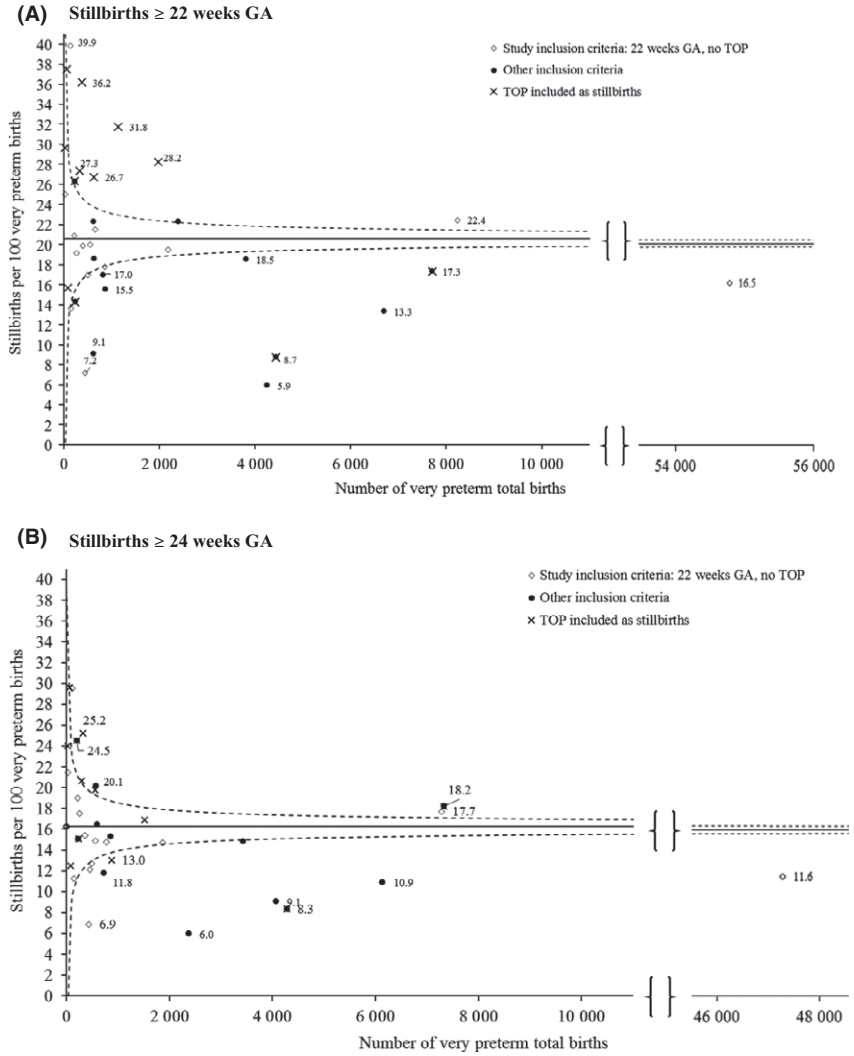

Figure 2. Stillbirths as a percentage of all singleton very preterm births in 30 countries in 2010 according to registration practices for births and deaths. (A) Stillbirths ≥22 weeks of gestation; (B) stillbirths ≥24 weeks of gestation.

Strengths and limitations

We had access to population-based data by completed week of gestation and plurality compiled using a common protocol.[1] Countries with varying gestational age or birthweight thresholds for recording stillbirth were identified. We also excluded TOP in countries where they are included in birth registries and identifiable, and flagged countries where TOP could not be removed. However, there were several limitations. We requested data using the best obstetric estimate of gestational age, but did not have further information on how this estimate was derived. Although ultrasound dating is the norm, various methods of gestational age assignment are likely used and may impact the preterm birth rate.[25,26] We also only had data from 1 year, which leads to random variation in countries with a small number of annual births. Finally, because our data were aggregated, we were unable to stratify by other factors that may affect the preterm birth rates such as maternal age, parity and socio-economic status.

Interpretation

Our results suggest an association between registration practices and VPT rates and rankings. Many countries with very low proportions of births 22–23 weeks of gestation were also those that used a registration criterion for stillbirths other than 22 weeks of gestation. Most countries register live births based on any sign of life, although practical and ethical difficulties can arise when assessing signs of life at the earliest gestational ages.[27–29] Regulations for stillbirths can vary between countries (i.e. parental leave allowance), and reporting may also differ based on the intent of sparing parents the burden

Table 2. Country rankings of singleton very preterm birth rates in 2010 using different gestational age and vital status criteria

Total 22–31 weeks*		Total 24–31 weeks (reference group)		Live 24–31 weeks	
Country	**Rate**	**Country**	**Rate**	**Country**	**Rate**
Iceland	**5.7**	**Iceland**	**5.2**	**Iceland**	**4.0**
Finland	**6.7**	**Finland**	**6.1**	**Finland**	**5.2**
Japan	**7.6**	**Japan**	**6.7**	**Japan**	**5.6**
Sweden	**7.7**	**Sweden**	**7.0**	France	5.7
Italy	**8.0*****	**Malta**	**7.2**	**Malta**	**5.7**
Slovakia	8.2	**Switzerland**	**7.3**	**Sweden**	**6.0**
Norway	**8.3**	**Norway**	**7.5**	Luxembourg	6.0
Malta	**8.3**	**Italy**	**7.7*****	**Switzerland**	**6.2**
Switzerland	**8.5**	Czech Republic	7.8	BE: Wallonia	6.4**
Ireland	8.7	Denmark	8.0	**Norway**	**6.6**
Portugal	8.8	France	8.0	BE: Flanders	6.7**
BE: Wallonia	9.0**	Slovakia	8.1	Czech Republic	6.8
Lithuania	9.0	BE: Wallonia	8.1**	Ireland	6.8
Denmark	9.1	Ireland	8.2	Lithuania	6.9
BE: Flanders	9.3**	Canada (2008)	8.2	Canada (2008)	7.0
Poland	9.5	BE: Flanders	8.3**	Denmark	7.0
Canada (2008)	9.5	Lithuania	8.3	**Italy**	**7.0*****
France	9.6	Poland	8.5	Slovenia	7.2
UK: Northern Ireland	9.8**	Luxembourg	8.6	Poland	7.3
Spain	10.0***	Portugal	8.7	Netherlands	7.3
Estonia	10.0	Netherlands	8.8	Portugal	7.4
Luxembourg	10.1	Estonia	9.2	Slovakia	7.5
Czech Republic	10.2	UK: Northern Ireland	9.3**	UK: Northern Ireland	7.9**
Cyprus (2007)	*10.2*	Slovenia	9.5	Estonia	8.2
Slovenia	10.6	Austria	9.6	*UK: Scotland*	*8.3***
Austria	10.8	Spain	9.6***	Austria	8.5
Germany	*10.9*	*Cyprus (2007)*	*9.8*	*UK: England and Wales*	*8.6***
UK: England and Wales	*11.0***	*Germany*	*10.0*	*Cyprus (2007)*	*8.3***
UK: Scotland	*11.1***	*UK: Scotland*	*10.4***	Spain	8.9***
Netherlands	11.5	*UK: England and Wales*	*10.5***	*Germany*	*8.9*
Romania	*11.5*	*Romania*	*11.4*	*Latvia*	*9.4*
Latvia	*12.0*	*Latvia*	*11.5*	*BE: Brussels*	*10.0***
United States	*14.1*	*United States*	*12.2*	*Romania*	*10.7*
BE: Brussels	*15.7***	*BE: Brussels*	*13.3***	*United States*	*10.8*

Data are given as Rates per 1000 births; Bold indicates countries with the lowest rates; Italic indicates countries with the highest rate for the reference group.
*Using lower threshold of 22 weeks of gestation, no TOP or national definitions.
**Data for Belgium and the UK provided by the region/constituent country.
***Incomplete registration before 180 days in Spain and Italy.

of having to report the death, or alternatively, feeling that parents would benefit from acknowledging that they had a baby which lived. These difficulties contribute to the wide variability in the proportion of periviable births registered as live versus stillbirth; the under-reporting of stillbirths also has an impact, as a large fraction of births at 22–23 weeks of gestation are stillbirths.

More generally, variations in the registration of stillbirths influence VPT rates, owing to the high proportion of stillbirths before 32 weeks of gestation. Antenatal screening practices and termination policies vary widely among countries,[30–32] and the prevalence of late TOP depends on those policies; some of the countries with high proportions of very preterm stillbirths were unable to remove TOP inflating overall figures. Terminations are not legal everywhere, meaning that births for lethal anomalies can be registered as stillbirths or neonatal deaths. TOP reporting can affect some countries more than others. In England and Wales, terminations cannot be distinguished from routine stillbirth statistics although a previous English study showed that late TOP for

congenital anomalies represent a relatively large proportion (17.1%) of births 22–26 weeks of gestation.[33] In Canada, there is some ambiguity between coding of TOP or congenital anomalies as the cause of death, which means that terminations are only excluded if recorded as the cause.

Our analyses show the importance of excluding perivable births and TOP from very preterm birth rate comparisons. However, our results also suggest that comparing rates starting at 24 weeks makes it possible to capture true variation between countries. Most countries can provide data on stillbirths starting at 24 weeks and this threshold is less sensitive to differences in the declaration of early neonatal deaths as stillbirths than a 22-week threshold.[11,14,16,34,35] Moreover, about 90% of live births will be at least 500 g at 24 weeks of gestation,[36] thus the criteria of 24 weeks enables comparisons with countries using a 500-g inclusion threshold for stillbirths. We also showed that even if there was under-reporting of stillbirths between 24 and 27 weeks of gestation in countries that do not record stillbirths starting at 22 weeks, this was unlikely to affect rates or rankings. Including spontaneous stillbirths in these comparisons is important to reflect the global burden of morbidity and mortality associated with very preterm birth; total and live VPT rates starting at 24 weeks correlated very strongly, and the associations between gestational-age-specific subgroup rates were strong.

Finally, we observed wide rate variations in countries like France and the USA where we do not suspect there would be registration issues given their lower registration thresholds at 22 weeks of gestation, capacity to exclude TOP and data coverage above 99%. Based on the rate least susceptible to reporting differences, live VPT rates at 24 weeks and over, two-fold differences were observed among countries with low (Iceland, Finland) versus high (the USA, Romania) rates. Differences in maternal risk profiles could explain true differences in underlying very preterm birth risks. The latest European Perinatal Health Report showed cross-country variations in maternal characteristics typically associated with preterm delivery rates, including age, smoking, pre-pregnancy body mass index and education.[1,37] However, studies comparing the USA with Canada, and France have shown that variations in risk of preterm delivery persisted even after adjustment for these sociodemographic characteristics.[38,39] Differences in health systems factors may be another explanation for the observed heterogeneity; up to 46% of very preterm singletons result from a provider-initiated delivery.[40]

Conclusions and recommendations

Our study answers the question—whether valid international comparisons are possible using routine data—with a qualified *yes*. We demonstrated the importance of adopting a standardised approach to these comparisons by excluding births at 22 and 23 weeks of gestation and TOP, and provided indicators to flag countries with less reliable data at early gestational ages. However, we also found wide differences in rates among countries with similar inclusion criteria and complete coverage of all births. Differences in these rates have wide-reaching implications for public health. Besides their impact on national perinatal mortality rates,[34,41,42] the health and financial burden of neurodevelopmental impairment is very high among very preterm survivors.[3,6,18,19] Medical advances have improved outcomes for these infants but preterm birth prevention, defined as effective medical interventions supported by policy initiatives, still constitutes a challenge.[43,44] The wide range of rates observed in countries with similar levels of development suggests that potentially modifiable population or healthcare factors and practices, such as induced preterm birth, merit further study. Regularly reported international data on very preterm births are needed to provide country-specific benchmarks for preterm birth prevention initiatives, to inform decision-making and to target future investments in health care and research.[45,46]

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MD, MSK and JZ conceived the study; MD carried out statistical analysis; AHM, LKS, KS, JLR, PDR, JR, PV, IZ, LS, MG, NM, SMD, and MRK provided data, contributed to the interpretation of the results and revised successive versions of the article. Members of the Euro-Peristat Scientific Committee were responsible for the provision, accuracy and interpretation of data in their country: they commented on the final version of the article. All authors approved the final article.

Details of ethics approval

This study used aggregated national indicators, ethical approval was not required.

Funding

This study was funded by grants from the European Commission for the Euro-Peristat project: 2010 13 01 and for the Bridge Health project: 664691. The funding agency was not involved in the study. MD received doctoral funding from Paris Descartes University, Paris, France. JLR received support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) T32 Predoctoral Training Program in Reproductive, Perinatal, and Pediatric Epidemiology under Award Number T32HD052460. NM was supported by the Japan Ministry of Health, Labor and

Welfare (H28-ICT-001) and the Japan Agency for Medical Research and Development (AMED-6013). LKS is funded by a National Institute for Health Research Career Development Fellowship. This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements

The authors acknowledge contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010. Please see Supplementary material, Appendix S1, for a full list of contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Stillbirths as a percent of singleton very preterm births by gestational age categories in 30 countries in 2010.

Figure S2. Very preterm singleton birth rates by gestational age categories in 30 countries in 2010.

Table S1. Routine data sources in 2010

Table S2. Sensitivity analysis to compare very preterm birth country rankings in 30 countries in 2010 if underreporting of stillbirths between 24 and 27 weeks of gestation

Appendix S1. List of contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010. ■

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Appendix

The Euro-Peristat Scientific Committee

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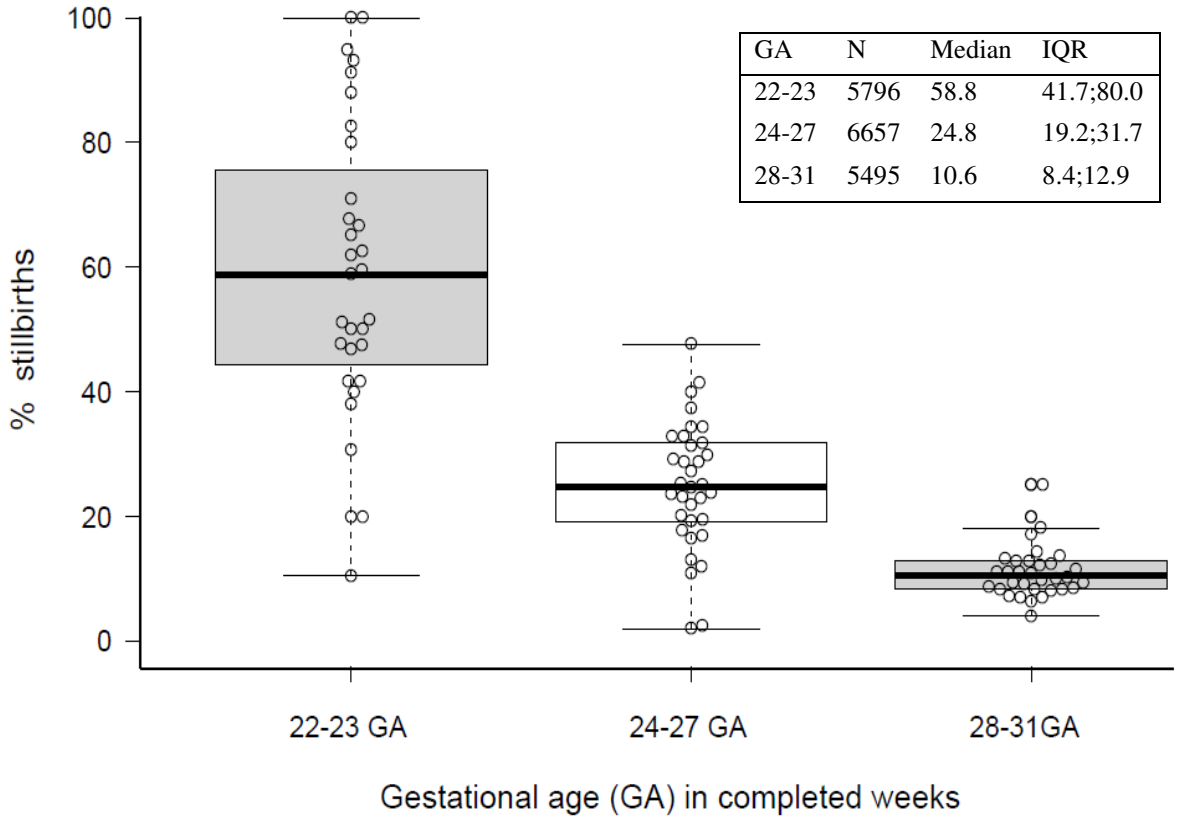
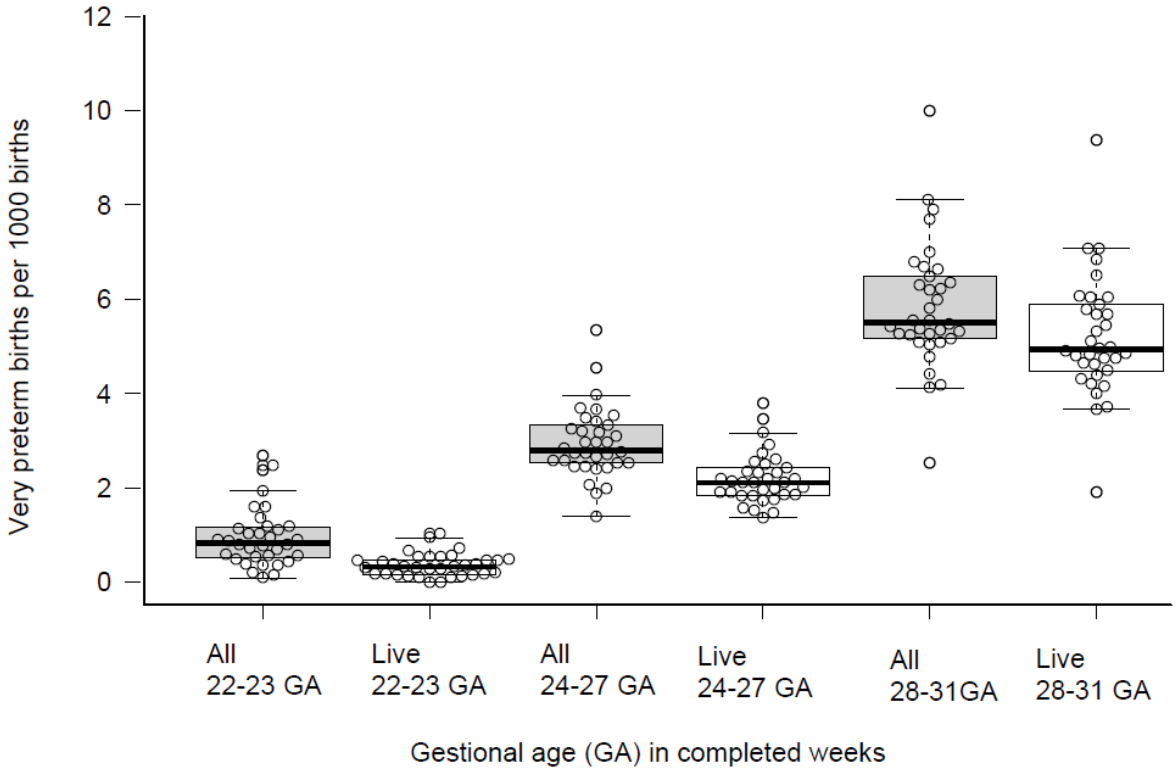


GA	N	Median	IQR
22-23	5796	58.8	41.7;80.0
24-27	6657	24.8	19.2;31.7
28-31	5495	10.6	8.4;12.9

NOTE: Center lines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; data points are plotted as open circles. N= 17 948 stillbirths

Figure S1. Stillbirths as a percent of singleton very preterm births by gestational age categories in 30 countries in 2010.



NOTE: Center lines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; data points are plotted as open circles. N= 88 845 live VPT births, 17 948 VPT stillbirths

Figure S2. Very preterm singleton birth rates by gestational age categories in 30 countries in 2010

Supplemental Table S1. Routine data sources in 2010

Country	**Data source/Institution**	**Type of data**	**Coverage**	**Completeness**
		P= Population H= hospital O= Other	C= Country O= Other	U = Unknown
Austria	Birth statistics	P	C	99%
BE: Brussels	Centre d'Epidémiologie Périnatale (CEpiP)	P	O: Brussels	± 100 %
BE: Flanders	Study Center for Perinatal Epidemiology (SPE)	H	O: Flanders	100%
BE: Wallonia	Centre d'Epidémiologie Périnatale (CEpiP)	P	O: Wallonia	± 100 %
Canada (2008)	Vital Statistics linked files, Statistics Canada	P	C	± 99.9%
Cyprus	Perinatal Health Survey 2007	O	C	31.5% representative sample
Czech Republic	Institute for Health Statistics and Information of the Czech Republic (UZIS CR)	P	C	99.3%
Denmark	The Medical Birth Register	P	C	± 100 %
Estonia	Estonian Medical Birth Register	H	C	100%
Finland	Medical Birth Register	P	C	100%
France	French National Perinatal Survey	P	C	99.6% representative sample
Germany	AQUA_German Perinatal Register	H	C	99.5%
Iceland	Medical Birth Register	P	C	99%
Ireland	National Perinatal Reporting System (NPRS)	P	C	100%
Italy	Birth certificates	P	C	84%
Japan	Vital Statistics Japan	P	C	± 100%
Latvia	Medical Birth Register	P	C	100%
Lithuania	Medical Date of Births	H	C	99%
Luxembourg	Perinatal Health Monitoring System	O	C	100%
Malta	National Obstetrics Information System	P	C	100%

Norway	Medical Birth Register of Norway	P	C	100%
Poland	Central Statistical Office	P	C	100%
Portugal	National Statistics - Live births and fetal, neonatal and infant deaths	P	C	100%
Romania	National Institute for Statistics demographic statistics for births	H	C	NA
Slovakia	National Health Information Center 2010	P	C	100%
Slovenia	National Perinatal Information System of Slovenia	H	C	100%
Spain	National Institute for Statistics (INE)	P	C	± 100 %
Sweden	Medical Birth Register	P	C	99.4%
Switzerland	BEVNAT, statistics of natural population change (vital statistics)	P	C	± 100%
The Netherlands	Netherlands Perinatal Register PRN	P	C	96%
United Kingdom: England and Wales	Civil Registration of births and deaths linked to NHS Numbers for Babies records	P	O: England and Wales	100%
United Kingdom: Northern Ireland	Child Health System	P	O: Northern Ireland	100%
United Kingdom: Scotland	Scottish Morbidity Record (SMR02)	H	O: Scotland	~98%
United States	U.S. Vital Statistics, Natality Public Use Files NCHS of the U.S. Centers for Disease Control and Prevention.	P	C	± 100%

Table S2. Sensitivity analysis to compare very preterm birth country rankings in 30 countries in 2010 if underreporting of stillbirths between 24 and 27 weeks of gestation.

Rates per 1000 births ≥ 24 weeks[1] Green = countries with the lowest rates; Red= countries with the highest rate for the reference group			
Total **24-31 weeks GA** reference group		**Total[2]** **24-31 weeks GA**	
Country	**Rate**	**Country**	**Rate**
Iceland	5.2	Iceland	5.2
Finland	6.1	Finland	6.1
Japan	6.7	Japan	6.7
Sweden	7.0	Sweden	7.0
Malta	7.2	Malta	7.2
Switzerland	7.3	Switzerland	7.3
Norway	7.5	Norway	7.5
Italy	7.7	Italy*	7.8*
Czech Republic	7.8	Czech Republic	7.8
Denmark	8.0	France	8.0
France	8.0	Denmark	8.0
Slovakia	8.1	Slovakia	8.1
BE: Wallonia	8.1	BE: Wallonia	8.1
Ireland	8.2	Canada	8.2
Canada (2008)	8.2	BE: Flanders	8.3
BE: Flanders	8.3	Lithuania	8.3
Lithuania	8.3	Ireland*	8.4*
Poland	8.5	Luxembourg	8.6
Luxembourg	8.6	Poland*	8.7*
Portugal	8.7	Netherlands	8.8
The Netherlands	8.8	Portugal*	8.9*
Estonia	9.2	Estonia	9.2
UK: Northern Ireland	9.3	UK: Northern Ireland*	9.5*
Slovenia	9.5	Spain*	9.7*
Austria	9.6	Austria*	9.8*
Spain	9.6	Cyprus (2007)	9.8
Cyprus (2007)	**9.8**	**Slovenia***	**9.9***
Germany	**10.0**	**Germany***	**10.2***
UK: Scotland	**10.4**	**UK: Scotland***	**10.8***
UK: England and Wales	**10.5**	**UK: England and Wales***	**10.9***
Romania	**11.4**	**Romania**	**11.4**
Latvia	**11.5**	**Latvia**	**11.5**
United States	**12.2**	**United States**	**12.2**
BE: Brussels	**13.3**	**BE: Brussels**	**13.3**

NOTE: (1) In green countries with the lowest rates (below the first quartile), and in red countries with the highest rates (above the third quartile) (2) Rates were corrected for 33% underreporting in stillbirths at 24-27 weeks GA.

Appendix S1. List of contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010.

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BJOG An International Journal of Obstetrics and Gynaecology

Sir,

The paper of Delnord et al. presents a dilemma in using routinely collected gestational age (GA) data especially regarding the inclusion of births at 22–23 weeks GA for international comparisons of very preterm (VPT) birth rates. In this paper VPT birth data from European countries were collected for the year 2010. As Croatia was not yet a member of the European Union, we would like to compare Croatian VPT birth data from the national medical birth register with the presented findings. From 2001 onwards, data on all live births (LB), irrespective of birthweight (BW) and GA, and stillbirths (SB) ≥22 weeks of GA or BW ≥500 g have been reported for routine health statistics, in contrast to national vital statistics data for LB, which were collected irrespective of GA and BW. Nonetheless, data from the medical birth register were similar to vital statistics for 99.9% of births.

A total of 43 419 newborns were born in the year 2010 in Croatia.[2] Among 41 024 singletons with known GA, there were 315 VPT births: 0.6‰ (15 LB and 10 SB) at 22–23 weeks, 2.6‰ (83 LB and 25 SB) at 24–27 weeks, and 4.5‰ (149 LB and 33 SB) at 28–31 weeks of GA. In 2010 for the 30 countries described by Delnord et al.[1] there were 106 793 VPT singleton births with averages as follows: 0.9‰ for 22–23 weeks of GA, 2.8‰ for 24–27 weeks of GA and 4.9‰ for 28–31 weeks of GA.

The VPT birth rate in 2010 in Croatia was 7.7/1000 total births, whereas the median singleton VPT rate among the 30 high-income countries analysed was 9.5 per 1000 births. Croatian rates were below the 25th centile (Q1 = 8.5‰) as in Iceland, Finland, Japan, Sweden, Italy, Slovakia, Norway and Malta. The proportion of periviable births (22–23 weeks GA) among all VPT births in Croatia was 7.9%, whereas Delnord et al. found variations of proportions between 0.7 and 23.4% among 30 countries. Stillbirths constituted 21.6% of all VPT births in Croatia, similar to the 20.6% average of the 30 analysed countries. After exclusion of periviable births (25), the percentage of SB among VPT births was 20.0%, only a slight difference from rates including VPT births at 22–23 weeks of GA. So, exclusion of periviable births from our results would not substantially influence the VPT birth rate. Data collected in Croatia represent the example of possible valid comparisons even when using routinely collected data since 2001, using World Health Organization (International Classification of Diseases, 9th revision) (WHO ICD-9) and the International Federation of Gynecology and Obstetrics (FIGO) (≥22 weeks GA) recommendations from 1979 to 1982, respectively.[3]

Although, the results of Delnord et al. indicated possible difficulties in comparisons of the VPT birth rates, it would be preferable to establish common rules for collecting all birth data, including VPT birth data. Results from the Euro-Peristat Project should encourage national agencies to collect data following the WHO ICD-9 and FIGO recommendations. Goldenberg and McClure also strongly suggest collecting all perinatal outcome data irrespective of GA or BW, whether born alive or stillbirth.[4] ■

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Accepted 22 February 2017.

DOI: 10.1111/1471-0528.14641

Authors' reply

Sir,

Our study was conducted as part of the Euro-Peristat project using data from 2010.[1] Croatia joined the Euro-Peristat network in 2014 and we are therefore pleased that Filipović-Grčić and Rodin provided Croatian data to complement our study and to add to the number of countries with available population-based data on very preterm (VPT) birth.[2]

In our study, we illustrated large variations in rates of birth at 22–23 weeks of gestation and the proportions of stillbirths among these births. Our results can be explained by differences in registration criteria for births and deaths in routine health information systems across high-income countries, as we also show, in addition to differences in practices for recording these periviable births.[3] We therefore concluded that using data on births starting at 24 weeks of gestation improves the comparability of estimates of VPT birth rates for international analyses.

Nevertheless, we fully agree with Filipović-Grčić and Rodin, that collecting information on all births starting at least at 22 weeks of gestation should be a key objective for perinatal health monitoring systems. The Euro-Peristat project compiles its perinatal health indicators using data on births starting at 22 weeks of gestation and if gestational age is missing for births ≥500 g. Collecting perinatal health data using a lower gestational age threshold and by individual weeks of gestation is essential for reflecting the full spectrum of maternal and child health birth outcomes, and pushing for the most comprehensive reporting.

Data on births at 22–23 weeks of gestation are scarce and one of the messages of our study is to encourage countries to improve and standardise reporting of births at very early gestational ages. Although there are few births at 22–23 weeks of gestation, they disproportionately contribute to the overall burden of perinatal mortality because of their very high rates of mortality. Furthermore, advances in neonatal medicine over the past decade have pushed back the limits of viability and an increasing number of these infants are being resuscitated,[4] although this remains an area where there is large international variability.[5] In this changing context having high-quality international data on these early births is particularly important.

We are hopeful that in the future, results from international comparisons of perinatal health data systems will encourage national agencies to improve the information available on these births, allowing for the best use of data collected on newborn health. ■

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Accepted 10 March 2017.

DOI: 10.1111/1471-0528.14642

Re: Long-term outcomes of transobturator tapes in women with stress urinary incontinence: E-TOT randomized controlled trial

Sir,

We agree with the data of Karmakar et al.[1] about long term complications of transobturator tapes in women with stress urinary incontinence. The data revealed 71.6% success rate, 4% groin pain, and 8% re-operation.

Common complaints after operation were vaginal discharge, groin pain, and hip pain. Gynaecologists cannot easily differentiate between severe complications and common complaints. Our findings will help gynaecologists find the complications.

A 54-year-old postmenopausal woman was admitted complaining of right hip pain and right thigh oedema. She had difficulty walking because of the hip pain. She had uncontrolled diabetes mellitus (DM), hypertension, and hypothyroidism. Pelvic examination revealed cervix motion tenderness. Examination revealed pain and tenderness in the lower abdomen and right leg. Urinalysis revealed trace amounts of urinary albumin and leukocytes, with a C-reactive protein (CRP) level of 12.01 mg/dL (normal is < 0.5 mg/dL), white blood cell count of 15 040/dL, haemoglobin concentration of 10.6 g/dL, and haematocrit of 31.8%. Magnetic resonance imaging revealed secondary myositis involving the right obturator internus and externus, adductor brevis and longus, and pectineus muscles. There was reactive fluid collection in the right hip joint. The patient was managed for infection and treated with antibiotics for 14 days. A fasciotomy and open wound debridement were performed after 7 days. At a second operation, the remnant mesh was removed from the thigh under ultrasonographic guidance, which revealed a subcutaneous foreign body in the medial aspect of the right inguinal region. Transobturator tape (TOT) is popularly used to manage urinary frequency. Rare reported complications of TOT include myositis of the thigh muscles and fistulas, and these can be severe.[2,3] A gynaecologist should warn the surgeon about the possibility of incomplete removal and severe complications in patients with chronic disease, such as our patient. Complete removal can be difficult, and pulling on the TOT can cause irritation, inflammation, and severe pain. Gynaecologists should be aware of these rare complications involving TOT removal. This patient had uncontrolled DM and hypertension. DM is a risk factor for inflammation. Urogynaecologists should be aware of potential problems in patients with chronic disease and advise such patients of possible rare complications of TOT removal. ■

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Chapter 5: Characterizing variations in the preterm birth rate

The most likely sources of variation in high-income countries are related to: maternal socio demographic status and behaviors, clinical practices and reproductive technologies, as well as broad environmental determinants (cf. Chapter 2). Recent research also showed that early term infants display odds of adverse outcomes similar to those of late preterm births, whereas full term births at 39-40 completed weeks are considered the lowest risk GA subgroup (19). Based on the premises that population exposures such as environmental factors will not only impact on mothers at high risk of early delivery but also on the overall population of childbearing women, our hypothesis was that preterm birth rate variations might reflect broader shifts in the GA distribution of births.

Therefore we studied associations between preterm birth and other indicators of the GA distribution: early term birth rates (37-38 weeks), and mean term GA (107) using data from 34 countries in 1996-2010. In 2010, the median rate of early term birth was 22.2% with a range between 15.6% and 30.8% and preterm birth rates varied between 4.1% and 8.2%, with a median of 5.5%. Relative rate variations for preterm and early term birth were comparable, and countries with high early term rates and lower mean GA were more likely to have high preterm rates. Strong associations between GA subgroups suggest that the risk of early delivery is not specific to PTB but shared across the gestational age continuum. The composite effect of population risk factors associated with PTB may result in broader GA shifts towards early delivery. Associations increased over time and results were similar for both spontaneous and provider-initiated births.

Our results have been published under the following citation:

Delnord M, Mortensen L, Hindori-Mohangoo AD., Blondel B, Gissler M, Kramer MR, Richards JL, Deb-Rinker P, Rouleau J, Morisaki N, Nassar N, Bolumar F, Berrut S, Nybo Andersen AM, Kramer MS, Zeitlin J, and the Euro-Peristat Scientific Committee; International variations in the gestational age distribution of births: an ecological study in 34 high-income countries, *European Journal of Public Health*, 2017 Sep 8. doi: 10.1093/eurpub/ckx131. [Epub ahead of print] ckx131

[Accepted 10th August, 2017]

European Journal of Public Health, 1–7

doi:10.1093/eurpub/ckx131

International variations in the gestational age distribution of births: an ecological study in 34 high-income countries

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Background: Few studies have investigated international variations in the gestational age (GA) distribution of births. While preterm births (22–36 weeks GA) and early term births (37–38 weeks) are at greater risk of adverse health outcomes compared to full term births (39–40 weeks), it is not known if countries with high preterm birth rates also have high early term birth rates. We examined rate associations between preterm and early term births and mean term GA by mode of delivery onset. **Methods**: We used routine aggregate data on the GA distribution of singleton live births from up to 34 high-income countries/regions in 1996, 2000, 2004, 2008 and 2010 to study preterm and early term births overall and by spontaneous or indicated onset. Pearson correlation coefficients were adjusted for clustering in time trend analyses. **Results**: Preterm and early term births ranged from 4.1% to 8.2% (median 5.5%) and 15.6% to 30.8% (median 22.2%) of live births in 2010, respectively. Countries with higher preterm birth rates in 2004–2010 had higher early term birth rates ($r > 0.50$, $P < 0.01$) and changes over time were strongly correlated overall (adjusted-$r = 0.55$, $P < 0.01$) and by mode of onset. **Conclusion**: Positive associations between preterm and early term birth rates suggest that common risk factors could underpin shifts in the GA distribution. Targeting modifiable population risk factors for delivery before 39 weeks GA may provide a useful preterm birth prevention paradigm.

Introduction

The typical length of pregnancy is 39–40 weeks, but annually 15 million infants are born preterm, defined as birth before 37 completed weeks of gestation.[1] Preterm birth is associated with adverse child health and long-term neurodevelopmental outcomes.[1] While medical advances have reduced mortality and morbidity risks among preterm infants over past decades, little progress has been made in preventing the incidence of preterm birth.[2] There are few effective interventions for preventing preterm delivery and, with the exception of programs promoting smoking cessation, they tend to target selected groups of high risk pregnancies, such as women with previous preterm deliveries in the case of progesterone or cervical cerclage.[2,3] However, differences in rates across high-income countries from 5% to 10%, as well as heterogeneous time trends,[4–6] suggest that there are modifiable population factors that affect preterm birth risk.[7]

Identifying population-wide exposures and designing policies to mitigate them could be facilitated by a broader focus on early delivery. Whereas preterm birth is associated with the greatest risks, recent research on early term births (37 and 38 completed weeks) also highlighted their elevated risks of adverse health outcomes compared to those born full term, at 39 or 40 weeks.[8] Given their larger numbers, early term births may provide studies with greater power to detect risk factors which influence changes in preterm birth rates but also impact on the population gestational age (GA) distribution.

Few studies have investigated international variations in the GA distribution,[9] and it is not known whether countries with higher preterm birth rates also have higher rates of early term births. If common risk factors affect earlier delivery across the GA spectrum, we would expect associations between preterm and early term birth rates across countries and across time. Furthermore, policies that successfully shift the GA distribution towards later delivery could reduce preterm births as well as early term births. We thus aimed to investigate variations in early term births and their association with preterm birth rates, and mean term GA in high-income countries.

Methods

Data sources

We used data from the Euro-Peristat project, which monitors a set of 30 perinatal health indicators in European countries using data available in national health information systems.[10,11] Data were also obtained for the United States (US), Canada and Japan as part of the PREBIC Epidemiology Working Group (www.prebic.org). Data from Australia were ascertained from the New South Wales Perinatal Data Collection.

The Euro-Peristat project collected aggregate data on all births starting at 22 weeks of GA in 2004 and 2010.[4] One of Euro-Peristat's Core indicators is the distribution of GA in completed weeks by vital status (stillbirths and live births) and multiplicity. The project also conducted a separate study on preterm birth for all live births by multiplicity and mode of onset and delivery for the years 1996, 2000, 2004 and 2008 in 19 countries.[5] The data collection sheets for the Euro-Peristat core indicators and the study on preterm birth were used to acquire data from the non-European countries in the PREBIC project (US, Canada, Japan) and Australia.

Data came from vital statistics, civil registers and medical birth registers in most countries and from a nationally representative survey of births in France[4] (Supplementary Appendix A). If countries could not provide national data, population-based data from geographically defined regions were accepted. Data for Belgium came from Brussels, Wallonia and Flanders; data from the United Kingdom were provided by England and Wales combined, Northern Ireland and Scotland; data from Germany came from the regions of Hesse, Lower Saxony and Bavaria in 2000, 2004 and 2008, but national-level data were available in 2004 and 2010. Data from Canada do not include births in the Province of Québec, and data from Australia were limited to the region of New South Wales, which represents one-third of annual births in Australia. In the US, births from California were excluded due to non-reporting of clinical estimates of GA before 2007. In France, data were from 1995, 1998, 2003 and 2010; in Canada and UK: England and Wales, from 2005 instead of 2004; and in Sweden from 2009 instead of 2008.

Study population

Our study population was all singleton live births with a GA of 22 weeks or over. We focused on singletons, because preterm birth rates are much higher for multiple pregnancies and multiple pregnancy rates differ widely among countries.[12] Stillbirths were excluded, as stillbirth data were not available in 1996, 2000, or 2008. GA data were available from 16 countries/regions in 1996, 20 in 2000, 29 in 2004, 22 in 2008 and 34 in 2010. Fourteen countries had data for all five years. Data on mode of onset of labor (i.e. spontaneous or provider-initiated delivery) were available for 12 countries in 1996, 14 in 2000, 15 in 2004 and 16 in 2008, but not in 2010 (participating years of data are available in Supplementary Appendix A).

Definitions

GA was requested based on the best available obstetrical estimate. In Europe, Canada, Australia and Japan, GA is derived from ultrasound and other prenatal assessments of gestational length. In the United States, birth certificates historically relied on a clinical estimate of GA, which included postnatal assessments. In 2003, a revised version of the birth certificate using only antenatal assessments (the obstetric estimate) was devised and by 2010, 35 states had adopted the 2003 revision;[13] for the analyses, we used either the clinical or the obstetrical estimate.

We assessed countries' GA distributions based on the following outcomes: rates of preterm (22–36 weeks) and early term births (37–38 weeks) and mean GA at term, excluding preterm births. We recoded births 42 weeks GA and over to 41 weeks, because countries differed in their policies for management of post-term pregnancies, and our focus was whether the pregnancy progressed to term.[14] Subgroup analyses were done for very preterm births (24–31 weeks) and moderate and late preterm births combined (32–36 weeks). Births at 22–23 weeks GA were not included in very preterm birth analyses due to the impact of differing registration practices on very preterm birth rates.[15] We also computed rates by mode of delivery. We identified indicated deliveries where the mode of onset was provider-initiated: i.e. induction of labour, or prelabour or elective caesarean delivery, based on national classifications.

Missing data

Overall, less than 2% of GA data were missing, except in Germany (missing 3% in 2000), Norway (10% in 1996) and Spain (11–20% from 1996 to 2010).[16] Similarly, less than 2% of mode of delivery onset data were missing. Observations with missing data were excluded from the analyses.

Analysis strategy

We summarized countries' GA distributions using descriptive statistics of preterm and early term birth rates including median, interquartile range (IQR), and mean GA at term calculated for each country/region, year of birth, and mode of delivery onset.

We used Pearson correlation coefficients to assess the magnitude of the associations between rates of preterm and early term birth in each study period and in time trends over the study periods.To investigate time trends, we calculated compound annual growth rates of preterm and early term births between data points; where compound rates allowed us to take into account differences in time periods for which GA data were available across countries.

The Pearson correlation coefficient was used because it can be adjusted for clustering in time series analyses based on Lorentz' formula.[17] The adjusted Pearson correlation coefficient is a marginal association measure derived from generalized estimating equations which remain valid under the clustered framework, and take account of informative cluster size. We examined the associations overall and by mode of onset of delivery. We also carried our sensitivity analyses using Spearman non-parametric tests, which do not rely on assumptions of normality. All data used for GA subgroup rates in 1996, 2000, 2004, 2008, 2010, and growth rates between periods are provided in Supplementary Appendix B.

Data were analysed using STATA 13.0 software (StataCorp LP, College Station, TX, USA), while adjusted analyses were conducted using R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows live singleton preterm (22–36 weeks) and early term (37–38 weeks) birth rates in 2010 in 34 countries/regions. In 2010 across 34 high-income countries and regions, preterm birth rates varied between 4.1% and 8.2%, with a median of 5.5%.

Table 1 Live singleton preterm (22–36 weeks) and early term (37–38 weeks) birth rates in 2010

Country: region	Code	*N*	GA in completed weeks		
			22–36%	37–38%	Mean GA at term
Austria	au	75 950	6.3	25.5	39.3
Australia: New South Wales	nsw	92 974	5.5	23.4	39.3
Belgium: Brussels	be_bu	23 731	6.2	23.6	39.3
Belgium: Flanders	be_fl	67 029	6.0	24.3	39.2
Belgium: Wallonia	be_wa	36 965	6.5	29.1	39.1
Canada (without Québec)	ca	270 401	6.3	25.3	39.2
Czech Republic	cz	111 616	6.1	21.9	39.3
Denmark	dk	60 667	4.9	18.1	39.6
Estonia	es	15 357	4.6	17.1	39.6
Finland	fi	59 318	4.3	16.1	39.6
France	fr	14 326	5.5	22.5	39.4
Germany	ge_ntl	611 864	6.5	27.3	39.3
Iceland	ice	4 751	4.1	15.7	39.6
Ireland	ir	72 707	4.2	15.6	39.7
Italy	it	527 845	5.7	28.3	39.2
Japan	ja	1 080 089	4.7	30.8	39.0
Latvia	lv	18 662	4.9	17.5	39.4
Lithuania	li	30 035	4.3	15.7	39.5
Luxembourg	lu	6 285	6.3	29.7	39.1
Malta	mt	3 856	5.4	30.7	39.0
Netherlands	ne	171 781	5.9	21.8	39.4
Norway	no	60 623	4.9	16.4	39.6
Poland	po	402 171	5.3	19.9	39.5
Portugal	pt	98 386	5.9	26.5	39.0
Romania	ro	208 325	7.6	23.6	39.1
Slovakia	sa	54 041	5.7	19.9	39.4
Slovenia	se	21 482	5.5	19.1	39.4
Spain	sp	382 136	5.9	22.4	39.4
Sweden	sw	111 474	4.7	18.3	39.6
Switzerland	ch	77 016	5.2	26.5	39.2
UK: England and Wales	uk_ew	696 087	5.6	18.1	39.6
UK: Northern Ireland	uk_ni	24 804	5.6	16.6	39.6
UK: Scotland	uk_scot	55 367	5.5	16.3	39.6
USA (without California)	usa	3 363 032	8.2	27.2	39.0

The median rate of early term birth was 22.2% with a range between 15.6% and 30.8%. Mean GA at term ranged between 39.0 and 39.7 weeks.

Variation was seen in both spontaneous and provider-initiated births. In 2008, between 2.8% and 5.1% of live births were spontaneous preterm births, whereas from 1.1% to 4.4% were provider-initiated (cf. Supplementary table S1). Even greater variation was seen in early-term births: between 9.8% and 16.6% for spontaneous births, and between 4.3% and 15.5% for provider-initiated births.

Figure 1 displays the associations between preterm birth rates and early term birth rates in 1996, 2000, 2004, 2008, 2010. The strength of the correlation ranged between $r = 0.55$ and $r = 0.58$ in 2004–2010 ($P < 0.01$) whereas in 1996 and 2000 the magnitude of the association was lower and not statistically significant; results using Spearman's rank test were similar. Japan was an outlier in all years, with low preterm birth rates and high early term birth rates. Without Japan, correlations were stronger (r=.57 to .75, $P \leq 0.01$ in 2000–2010).We also studied countries with data available in all five study years (Supplementary table S2) and found similar results. Finally, we looked at associations for spontaneous and indicated deliveries separately and observed similar trends, although results were significant only for provider-initiated deliveries (cf. Supplementary figures S1A and S1B).

Associations between preterm birth rates and mean GA at term are shown in figure 2. Preterm birth rates were negatively correlated with mean GA at term in all years, with significant correlation coefficients of -0.51 in 2004, -0.58 in 2008 and -0.68 in 2010; in 1996 and 2000 however, the correlations were lower and were non-significant. Results using Spearman's rank test were similar.

Figure 3 illustrates the correlations between compound annual preterm and early term growth rates across the periods in our study, representing 83 time points from 29 countries/regions with data in at least two years. Temporal changes in preterm and early term birth rates were strongly correlated (adjusted Pearson' $r = 0.55$, $P < 0.01$). Although annual changes were more heterogeneous for provider-initiated births than for spontaneous births, correlations by delivery mode of onset for spontaneous and indicated births were similar (cf. Supplementary figure S2A and S2B). Changes in indicated preterm deliveries were not significantly correlated with changes in spontaneous early term deliveries (adj-Pearson's $r = 0.11$, $P > 0.05$, $N = 42$), nor were changes in spontaneous preterm deliveries significantly correlated with changes in indicated early term deliveries (adj-Pearsons' r= -0.32, $P > 0.05$, $N = 42$).

In preterm subgroup analyses, very preterm birth rates (24–31 weeks) were not correlated with early term births or mean GA at term in 1996–2010. Moderate and late preterm births (32–36 weeks) were positively correlated with early term births however (adj-Pearson's $r = 0.56$, $P < 0.01$, and negatively correlated with mean GA at term (r ranging from -0.6 to -0.7, $P < 0.01$ in 2004–2010 (cf. Supplementary table S3).

Discussion

Main findings

We found that early term birth rates varied by a factor of 2, comparable to the relative variation in preterm birth rates although higher in absolute terms: up to 15%. Countries with high early term rates and lower mean GA were more likely to have high preterm rates. These associations increased over time, especially from 2004 onwards. Time series results were similar for spontaneous and provider-initiated births, but cross-sectional results were

Figure 1 Associations between preterm birth rates (<37 weeks) and early term birth rates (37–38 weeks) in 1996, 2000, 2004, 2008, 2010. Note: For country codes see table 1. 'ge' refers to German data from the regions of Hesse, Lower Saxony and Bavaria in 2000, 2004 and 2008; 'ge_ntl' refers to national data available in 2004 and 2010

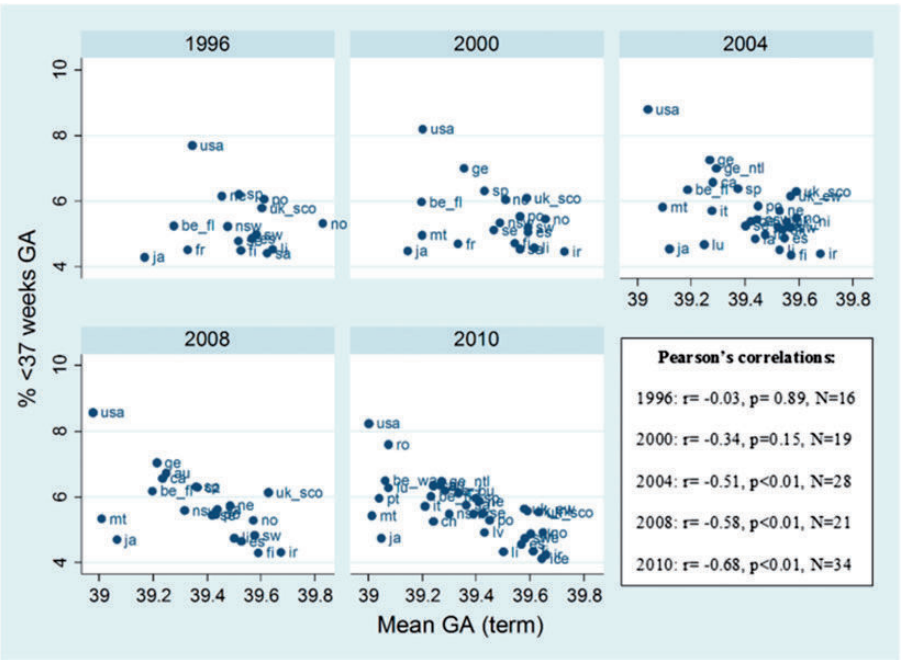

Figure 2 Associations between preterm birth rates (<37 weeks) and mean GA at term (37–41 weeks GA) in 1996–2010. Note: For country codes see table 1. 'ge' refers to German data from the regions of Hesse, Lower Saxony and Bavaria in 2000, 2004 and 2008; ge_ntl refers to national data available in 2004 and 2010

significant only for provider-initiated births. Finally, these associations were observed for moderate and late preterm births, but not for the sub-group of very preterm infants born before 32 weeks of GA.

Strengths and limitations

Our study's strengths include the use of population-based data on births at each completed week of gestation compiled using a common protocol for a large number of high-income countries from North America, Europe and Asia-Oceania. Data available from several years also allowed us to study time trends, and we adjusted for informative clustering of rates within countries in our time series analyses. Compound annual growth rates took into account relative changes in risks over differing time periods, and smoothed year-to-year volatility in preterm and early term birth rates.

One limitation was that although we requested data using the best obstetric estimate of GA, we had no further information on how that estimate was derived. Ultrasound dating was the norm, but other

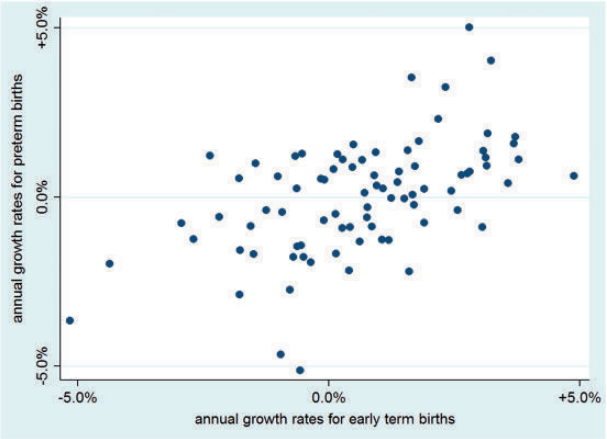

Figure 3 Associations between annual growth rates for preterm and early term births between 1996 and 2010. Note: Live births: adjusted Pearson's $r = 0.55$, $P < 0.01$; $N = 83$

methods of GA assignment were likely used and could impact estimates of both the preterm and early term birth rates.[18] Also, we had data on mode of delivery onset from fewer countries, as such data are not always collected in routine data systems. In Japan, for example, the absence of data on delivery onset limited further exploration of the high relative rates of early term vs. preterm births. Moreover, differences in definitions may affect the comparability of rates of spontaneous and indicated deliveries across countries.[4,19] Finally, since our data were aggregated, we were unable to stratify by other factors that may affect the preterm birth rate, including maternal age, parity, smoking and socioeconomic status.

Interpretation

Our data showing an association between early term and preterm births suggest that variations in preterm birth rates reflect, a more general shift in the GA distribution. Overall, we observed robust correlations between rates of preterm and both early term births and mean GA at term in time series analyses, which are less sensitive than cross-sectional analyses to varying definitions among countries. Cross-sectional correlations were not significant in 1996 and 2000, and for spontaneous-onset births in all years. The absence of associations in those years could be due to fewer countries with data, or to more recent changes. The absence of an association between very preterm and early term births may reflect differences in both etiology and practices for this sub-group.

GA subgroup rate associations across countries suggest that variation in risk factors for preterm birth may influence early delivery risk across the GA continuum. Maternal characteristics such as maternal age, smoking during pregnancy and BMI, are known to differ among high-income countries[20] and have been found to affect preterm birth trends within countries,[21–23] as well as socio-demographics factors such as maternal educational level and migrant status.[24] Environmental factors may also partially explain our findings. Policies to reduce exposure to secondary smoke have been found to correlate with reductions in the preterm birth rate in Belgium,[25] and in preterm and early term deliveries in Switzerland.[26] The impact of chemical exposures and air pollution on duration of gestation is of increasing interest although more research is needed on the underlying physiological mechanisms.[27,28] In a recent population-based study from Canada, associations of ambient air pollution with preterm birth were stronger among women with pre-existing diabetes, asthma and preeclampsia, suggesting that environmental factors interact with other population characteristics.[29]

Clinical practices related to indicated deliveries also likely contribute to our findings. Studies have shown wide variations in rates of obstetric intervention for subgroups at higher risk of intervention,[19] and throughout the GA continuum.[30] In New South Wales, a decreasing GA from 1994 to 2009 was associated with decreases in spontaneous birth and increases in early term birth and provider-initiated deliveries.[31] In the US, changes in the use of obstetric interventions have been studied as drivers of variation in the preterm birth rate,[32] and recommendations to decrease provider-initiated deliveries before 39 weeks have been linked to decreases in late preterm and early term birth.[9,33]

Guidelines related to screening, antenatal care and the management of pregnancy complications are different across countries and evolve over time; these may contribute to rate differences, in particular for provider-initiated births. For example, gestational diabetes will increase the risk of indicated preterm or early term delivery, but not all countries offer routine screening. Policies related to the timing delivery aim to maintain low rates of perinatal and maternal morbidity and mortality overall, but these also change over time which could contribute to variation in GA subgroup rates.

Finally, methods of GA estimation and the more frequent use of ultrasound for pregnancy dating could impact on GA subgroup trends. Some studies find that US dating increases preterm birth rates (because LMP estimates assume all women have a 28 day cycle, whereas the average is slightly longer),[34] while others have documented decreases in preterm birth (due to the elimination of erroneous GA).[35] The determination of GA is an important area for further research into cross-national variation in preterm and early term rates.[6]

Proposals for research and practice

GA at delivery is a strong determinant of perinatal and child health. Our findings show that variations in preterm and early term birth rates and trends tend to co-occur in most high-income countries, suggesting a common aetiology for early delivery.[34,35] These results warrant the evaluation of risk factors affecting both preterm and early term birth as opposed to targeting the highest-risk group of preterm births only. Based on the premises of Rose's population approach to the prevention of disease: changes in mean level of exposures and clinical practices may explain the observed heterogeneity in preterm and early term birth rates over time within, and among countries.[36] This carries implications for research and programme evaluation, in particular for the choice of outcome variables.

A population-based approach to early delivery prevention is related to mitigating demographic, behavioral and environmental risks in the general population, as well as evaluating the impact of clinical practices. Moreover, by focusing on shifting determinants of earlier birth among the low-risk majority it may be possible to achieve a similar impact on higher-risk groups as well, in line with a stewardship model of public health that is both ethical and efficient.[37] A 'population vision' of preterm birth prevention could also potentially link more global initiatives to reduce unnecessary obstetric interventions[38] to those intended to reduce preterm birth.

In conclusion, we observed wide variation in early term birth rates across high-income countries which were associated with preterm birth rates cross-sectionally and over time, with the exception of very preterm births. Our results suggest that a more general focus on identifying, designing and implementing interventions to target modifiable population-level risk factors for preterm as well as early term deliveries may provide a useful prevention paradigm.

Acknowledgements

The authors acknowledge contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010. Please see Supplementary Appendix C, for a

full list of contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010.

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Project coordination: Jennifer Zeitlin, Marie Delnord, Ashna Hindori-Mohangoo.

Supplementary data

Supplementary data are available at *EURPUB* online.

Funding

This study was funded by grants from the European Commission for the Euro-Peristat project: 2010 13 01 and for the Bridge Health project: 664691. The funding agency was not involved in the study.

Marie Delnord received doctoral funding from Paris Descartes University, Paris, France.

Jennifer L Richards received support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) T32 Predoctoral Training Program in Reproductive, Perinatal and Pediatric Epidemiology under Award Number T32HD052460.

Naho Morisaki was supported by the Japan Ministry of Health, Labor and Welfare (H28-ICT-001) and the Japan Agency for Medical Research and Development (AMED-6013).

Conflicts of interest: none declared

Key points

- There are wide variations in early term birth rates across high-income countries which are associated with preterm birth rates over time, with the exception of very preterm birth.
- Positive associations between preterm and early term birth rates suggest that common risk factors could underpin shifts in the GA distribution.
- Targeting modifiable risk factors for delivery before 39 weeks GA broadens the scope of current preterm birth prevention strategies and interventions.

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Supplemental Table S1. Preterm (<37 weeks) and early term (37-38 weeks) birth rates by mode of delivery onset in 2008 in 16 countries

	Gestational age (GA) in completed weeks				
	N	Spontaneous births		Indicated births	
Country		<37 weeks %	37-38 weeks %	<37 weeks %	37-38 weeks %
Australia: New South Wales	92 813	3.3	11.6	2.2	11.4
Belgium : Flanders	66 672	4.2	14.7	2.0	11.0
Canada (without Québec)	273 178	5.1	14.5	1.5	11.1
Czech Republic	114 722	4.4	16.6	1.9	4.8
Estonia	15 507	3.6	10.8	1.1	7.4
Finland	57 887	3.2	11.9	1.1	4.8
France	14 326	2.8	13.7	2.6	8.8
Germany: 3 Länders	208 457	4.0	14.2	3.0	12.7
Lithuania	30 510	3.2	11.7	1.5	4.3
Malta	4020	4.2	14.1	1.1	15.5
Netherlands	170 255	3.9	12.9	1.8	7.4
Norway	59 075	3.1	11.7	2.2	6.6
Slovenia	21 050	4.2	14.6	1.3	4.5
Sweden	105 855	3.1	11.7	1.7	6.8
UK : Scotland	56 468	4.8	9.8	1.3	6.7
USA (without California)	3 563 722	4.1	14.3	4.4	15.1

Supplemental Table 2. Correlations between preterm and early term birth rates in 1996,2000,2004,2008,2010 in countries with data available in all five years (N=14)

Year	Pearson's r, p
1996	0.22, p=0.43
2000	0.44, p=0.12
2004	0.56, p<0.05
2008	0.53, p<0.05
2010	0.53, p=0.05

Supplemental Table 3. Pearson and adjusted-Pearson correlations between preterm subgroups, early term births, and mean GA at term

Table S3A. Associations between very preterm, moderate and late preterm, and early term growth rates between 1996 and 2010, N= 83

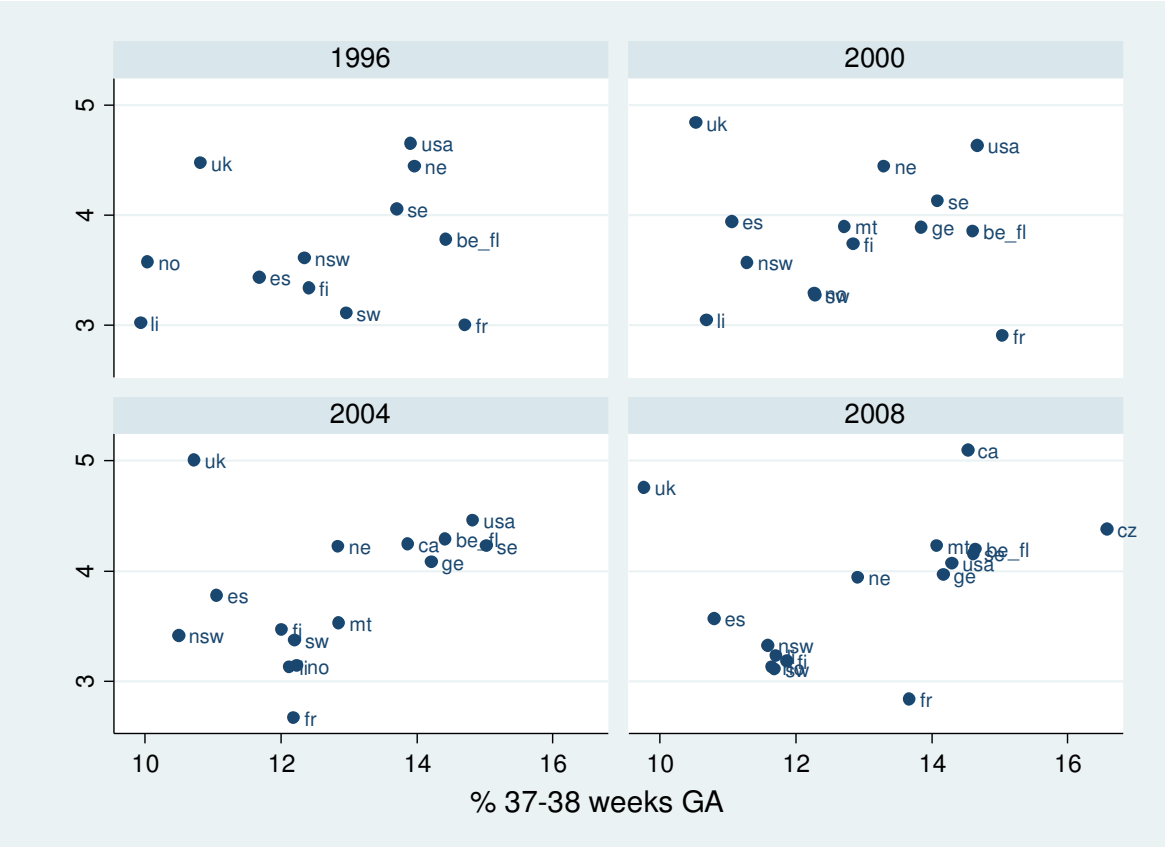
Gestational age in completed weeks (GA)	Very preterm births VPT: 24-31 weeks GA	Early term births ET: 37-38 weeks GA
Very preterm births	-	adj-r=0.05, p=0.75
Moderate and late preterm births MLP: 32-36 weeks	adj-r=0.06, p=0.83	adj-r=0.56, p<0.01

Note: Associations are based on annual growth rates in 1996-2010 (% per year)

Table S3B. Pearson correlations between very preterm, moderate and late preterm birth rates, and mean GA at term in 1996-2010

	Year				
Gestational age in completed weeks	1996 (N=16 Countries)	2000 (N=19)	2004 (N=28)	2008 (N=21)	2010 (N=34)
VPT: 24-31 weeks GA	r=0.41, p=0.12	r=0.20, p=0.40	r=0.07, p=0.72	r=-0.35, p=0.11	r=-0.15, p =0.39
MLP: 32-36 weeks GA	r= -0.14, p=0.61	r= -0.42, p=0.08	r=-0.58, p<0.01	r=-0.59, p<0.01	r=-0.72, p<0.01

Supplemental Figure S1A. Associations between spontaneous preterm and early term birth rates in 1996, 2000, 2004, 2008.

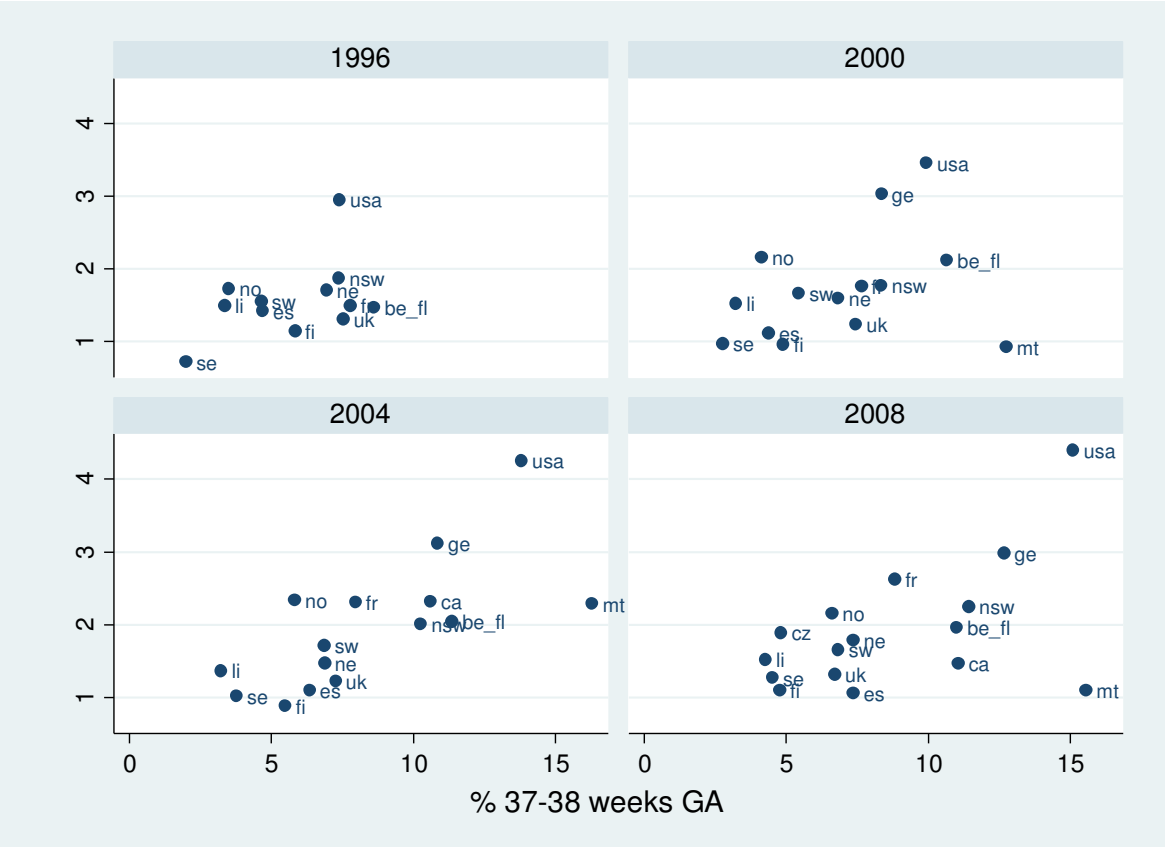


Note: Pearson's correlation coefficients:

1996: r=0.21, p=0.52, N=12; 2000: r= 0.03, p=0.92, N=14

2004: r= 0.35, p=0.21, N=15; 2008: r=0.39, p=0.13, N=16

Supplemental Figure S1B. Associations between indicated preterm and early term birth rates in 1996,2000,2004,2008

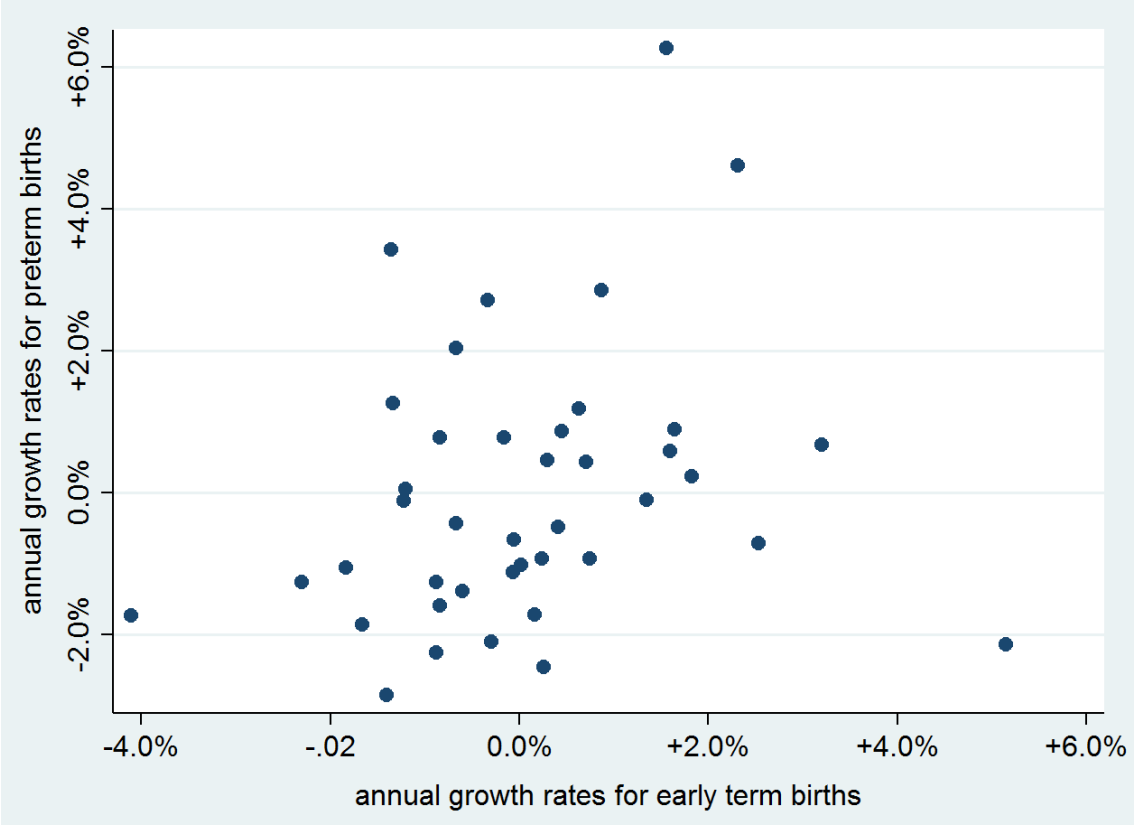


Note: Pearson's correlation coefficients:

1996: r=0.42, p=0.17, N=12; 2000: r=0.33, p=0.25, N=14

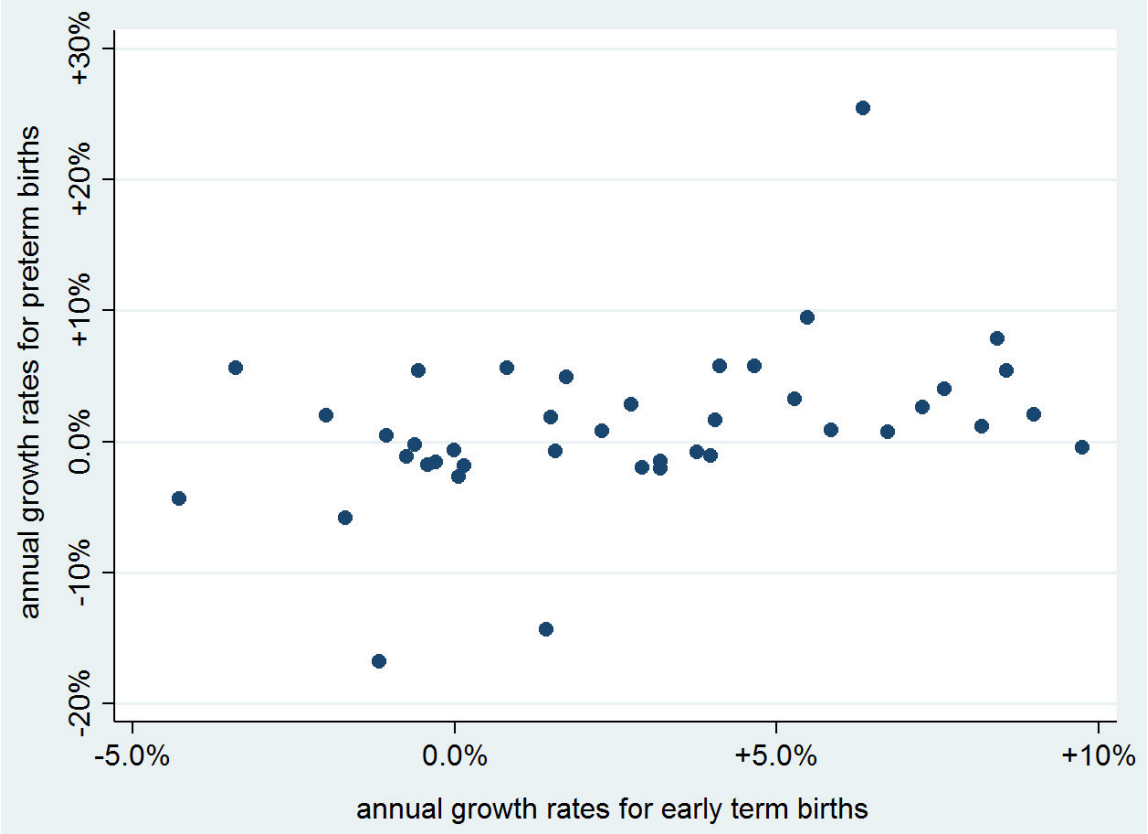
2004: r=0.70, p<0.01, N=15; 2008: r= 0.52, p<0.05, N=16

Supplemental Figure S2A. Associations between annual growth rates for spontaneous preterm and early term births between 1996 and 2008



Note: Spontaneous births: adjusted Pearson's r=0.32, p<0.05; N=41

Supplemental Figure S2B. Associations between annual growth rates for indicated preterm and early term births between 1996 and 2008.



Note: Indicated births: adjusted Pearson's r =0.40, p<0.01; N=41

Chapter 6: Targets for early delivery prevention

We showed that broad population characteristics (cf. Chapter 2) are likely to explain differences in the preterm birth rate between countries, and underpin shifts in the preterm birth rate within countries (cf. Chapter 5). When a standardized protocol is used to account for artefacts and for multiple births (cf. Chapter 4), the remaining heterogeneity is likely related to mothers' socio-demographic characteristics, obstetric history and behaviors. Because, our previous data were aggregated, we could not identify which population characteristics might have the greatest impact on the global preterm birth rate, and the wider GA distribution. In this chapter, we have identified potential target exposures for early delivery prevention using population-based data from France in 2010.

This work has been submitted to BMJ Open. The original manuscript is provided here; a revision was requested by the editors on August 24th, 2017.

Introduction

Preterm birth, defined as birth before 37 weeks of gestation, is a leading cause of perinatal mortality and morbidity. Preterm infants represent 60% of all neonatal deaths and 75% of all infant deaths (16). They are at risk of short and long-term neurocognitive and motor impairments, and display higher rates of chronic disease and premature death compared to term infants (16, 126). The prevention of preterm birth is a global priority, however preterm births are not the only gestational age subgroup at risk of adverse health outcomes(4). Compared to being born full term, defined as between 39 and 41 weeks, early term birth at 37 and 38 weeks is associated with higher risks of neonatal mortality, more intensive care unit admissions (98), and higher health-related costs well into childhood for obstructive airway diseases, visual and motor disabilities (52).

There are large differences in rates and trends of preterm and early term births among countries with similar levels of development (1)(87, 124). In Europe in 2010, preterm birth rates ranged between 4.1% and 8.2% while early term rates ranged between 15.6% and 30.8% (1); such heterogeneity across countries suggests that rate reductions may be possible. However, despite the significant public health burden (27, 52, 56), little progress has been made in decreasing the number of these early births (22, 63, 87). The latest French recommendations for the prevention of spontaneous preterm birth focus on smoking cessation and on interventions for women with high risk pregnancies (i.e. cerclage, progesterone), but conclude that high quality evidence does not exist for other preventive strategies (99); this is partially due to the low predictive accuracy of diagnostic tools (22). As for early term birth, prevention efforts are recent, with a focus by professional societies in the United States on the reduction of indicated early term deliveries for non-medical reasons (5).

More research on the etiology of early delivery is required to orient prevention efforts and practice. We know that early term and late preterm births both have worse neonatal outcomes compared to full term births (19), but we do not know if maternal characteristics related to preterm birth risk (16, 22, 29, 84) are also related to early term birth. Thus in this study we aimed to identify population determinants of preterm and early term birth taking into consideration mode of onset of delivery, i.e. spontaneous or indicated, using nationally representative data on births from the French National Perinatal Survey in 2010.

Materials and Methods

The French National Perinatal Survey 2010 (Enquête Nationale Périnatale, ENP) is a study based on a representative sample of births in Metropolitan France. Data were collected on live and stillbirths starting at 22 weeks of gestation or weighing at least 500g over the course of one week in public and private maternity units (18). We studied singleton pregnancies ending in a live birth with a gestational age of 22 weeks or over (N=14,326 pregnant women in 2010).

Multifetal pregnancies and stillbirths were excluded because of differences in delivery practices and etiology for these births.

Survey items on mothers' demographic characteristics (e.g. maternal age, parity), socioeconomic status (e.g. level of education), prenatal care and behaviors were collected during interviews in the postpartum ward. Other data on the delivery and newborn health were abstracted from the medical records. We defined indicated deliveries as those with a provider-initiated mode of onset, i.e. either induction of labor or prelabor cesarean section.

Our main outcomes were preterm and early term birth. These were defined respectively as births 22-36 completed weeks of gestation and 37-38 completed weeks overall and by mode of onset (spontaneous or indicated). Gestational age was based on the best obstetrical estimate. In France, nearly all women have a first trimester ultrasound for dating the pregnancy (18).

We selected risk factors based on a scoping review of the scientific literature, including recent research on preterm birth risk factors in France (84). Some preterm birth exposures that were available in the French National Perinatal Survey were omitted from our study because of their low prevalence in the sample (i.e. use of fertility treatments and diabetes, <4% and <2% respectively).

We included the following variables in our analysis: maternal age (<20, 20-24, 25-29, 30-34, >=35 years old), parity (1,2-3,4+), previous preterm birth, nationality (French, Other European, North African, Sub-Saharan African, Other), maternal height presented in quartiles (Q1: 100-160cm, Q2: 161-165cm, Q3: 166-168cm, Q4:169-190cm), pre-pregnancy body mass index (defined as underweight, normal, overweight, and obese women for BMIs <18.5, 18.5-24.9, 25-29.9,≥30 respectively), level of education, and smoking during the third trimester. Level of completed education was defined based on the ISCED 2011 classification: low educational level ISCED 0-2 (i.e. up to lower secondary education completed), medium

educational level ISCED 3-5 (i.e. upper secondary education or short cycle tertiary education completed), high educational level ISCED 6-7 (Bachelors' equivalent or higher) (109).

Analysis strategy

We first compared the distributions of preterm and early term births by maternal characteristics. We included all maternal exposures hypothesized to be associated with preterm delivery in the multivariate analyses (84). We used multinomial regression to estimate preterm and early term birth adjusted odds ratios and their 95% confidence intervals by maternal characteristics using births reaching full term (i.e. births 39 weeks and over) as the reference. In the mode of onset analyses, we computed odds of spontaneous and indicated preterm and early delivery using the same full term reference population (i.e. all births 39 weeks and over, regardless of mode of onset). Data were analysed using STATA 13.0 software (StataCorp LP, College Station, TX, USA).

There were 14 326 live singleton births in the survey of which 65 were missing GA data. We had less than 1% missing data on mode of onset of labor (i.e. spontaneous or provider-initiated delivery) and less than 5% missing sociodemographic data (i.e. nationality and level of education). There were 4% missing data on previous preterm birth and 6% missing on anthropometric characteristics (i.e. height or BMI). Although individual proportions of missing data were low, complete cases were only 86% of the total and therefore we imputed missing values (except the outcome) using multivariate imputation by chained equations. We performed 100 imputations using all available covariates (49). Descriptive and multivariate analyses were done on the imputed dataset.

Results

Table 1 provides descriptive statistics on our sample. We included 14 261 live singleton pregnancies with GA data available. The overall rate of preterm birth was 5.5% and early term birth was 22.6%. In the reference population of women with a full term birth, 2.4% were aged under 20 and 18.3% over 35 years of age; 44.1% were primiparous and 6.9% were parity 4 or more; 2.2% had a previous preterm birth, 7.8% were underweight, 9.4% were overweight and 16.4% smoked in the 3rd trimester of pregnancy. The risk profiles of mothers with a preterm and early term infant were different. These mothers were more likely to be older, have a previous preterm birth, be of shorter stature, with a lower level of education, and smoke. Mothers with a preterm birth were more likely to be primipara whereas mothers with an early term birth were more likely to be multipara, compared to mothers with a term birth.

In multinomial multivariable models, most of these associations persisted; common population determinants for preterm and early term birth were: a previous preterm birth, shorter stature, underweight, sub-Saharan nationality, and a low level of education. There were some differences in the impact of these risk factors: a previous preterm birth was a stronger risk factor for preterm birth than early term birth (aOR 8.2 vs. 2.4 respectively); maternal underweight and Sub-Saharan nationality were also stronger risk factors for preterm compared to early term birth. Primipara were at risk for preterm birth only (aOR 1.8 [1.5-2.2]), whereas grand multipara (parity 4+) were at higher risk of early term birth. After adjustment, advanced maternal age, and smoking during the third trimester were no longer associated with increased risks of delivery before 39 weeks.

Table 1: Associations between maternal characteristics and risks of preterm and early term birth

		<37 wks GA %	37-38 wks GA %	≥39 wks GA %		<37 weeks GA		37-38 weeks GA	
	N	N=782	N=3010	N=10269	p[a]	aORs[b]	95% CI	aORs[b]	95% CI
Maternal age									
<20 years	346	3.9	2.3	2.4	0.005	1.0	0.7-1.6	0.9	0.7-1.2
20-24 years	2078	16.3	14.5	14.5		0.9	0.8-1.2	1.0	0.9-1.2
25-29 years	4737	32.8	31.7	33.7		1	-	1	-
30-34 years	4380	27.9	30.1	31.1		1.0	0.8-1.2	1.0	0.9-1.1
>=35 years	2720	19.1	21.4	18.3		1.1	0.9-1.4	1.2	1.0-1.3
Parity					<0.001				
1	6165	49.8	38.9	44.1		1.8	1.5-2.2	0.9	0.8-1.0
2-3	6980	39.8	50.8	49.1		1		1	-
4+	1116	10.4	10.3	6.9		1.2	0.9-1.6	1.2	1.1-1.4
Previous preterm birth					<0.001				
No	13740	86.6	94.1	97.8		8.2	6.2-10.7	2.4	2.0-3.0
Yes	521	13.4	5.9	2.2		1	-	1	-
Maternal height					<0.001				
Q1: 100-160 cm	4365	37.7	34.6	28.8		1.4	1.1-1.7	1.4	1.2-1.6
Q2: 161-165 cm	4143	25.9	29.9	29.0		1.0	0.8-1.2	1.2	1.1-1.4
Q3: 166-168 cm	2440	15.2	15.2	17.9		0.9	0.7-1.2	1.0	0.9-1.2
Q4: 169-190 cm	3313	21.3	20.4	24.3		1	-	1	-
Pre-pregnancy BMI					0.307				
<18.5	1177	12.9	8.5	7.8		1.7	1.3-2.2	1.1	1.0-1.3
18.5-25.9	9190	59.9	63.6	65.0		1	-	1	-
25-29.9	2472	15.5	16.6	17.7		0.9	0.7-1.1	0.9	0.8-1.0
>=30	1422	11.7	11.2	9.4		1.2	1.0-1.6	1.1	1.0-1.3
Nationality					0.043				
French	12360	84.0	86.3	87.0		1	-	1	-
Other European	470	4.2	3.3	3.2		1.2	0.8-1.8	1.0	0.8-1.2
North African	685	4.9	4.4	4.9		1.1	0.7-1.5	0.8	0.7-1.0
Sub-Saharan Africa	392	4.5	3.3	2.4		1.8	1.2-2.6	1.3	1.0-1.6
Other	354	2.5	2.7	2.4		1.0	0.6-1.6	1.1	0.8-1.4
Level of education									
Low ISCED 0-2	4054	37.5	31.9	26.7	<0.001	1.7	1.3-2.1	1.2	1.1-1.4
Medium ISCED 3-5	5883	38.8	40.6	41.7		1.2	1.0-1.5	1.1	1.0-1.2
High ISCED 6+	4324	23.7	27.6	31.7		1	-	1	-
Smoking n° cigarettes/day during the 3rd trimester					<0.001				
0	11814	79.1	81.4	83.6		1	-	1	-
1-9 cigarettes	1757	13.9	12.8	12.1		1.0	0.8-1.3	1.0	0.9-1.2
>=10 cigarettes	690	7.0	5.8	4.4		1.3	0.9-1.8	1.1	0.9-1.4

a. F-test b. Adjusted Relative Risk Ratio

In Table 2, we display the associations between spontaneous preterm, and early term births by maternal characteristics. Out of all births, 2.8% were spontaneous preterm births and 13.6% were spontaneous early term births. Common risk factors were: a previous preterm birth, short stature, maternal underweight, foreign nationality (i.e. Other European), and a low level of education. There were some differences in the impact of these risk factors. Underweight was a stronger risk factor for spontaneous preterm than early term birth: aOR 1.9[1.4-2.6] vs aOR 1.3[1.1-1.5] respectively, and overweight women displayed a reduced risk of spontaneous early term delivery. Primipara were at risk of preterm birth but not early term birth. Smoking during the third trimester was associated with a moderately increased risk of spontaneous preterm delivery, although the confidence interval included 1: aOR 1.5[1.0-2.2]. The aOR was lower and non-significant for early term birth: 1.2[0.9-1.5].

Table 2: Associations between maternal characteristics and risks of spontaneous preterm and early term birth

	<37 weeks GA % N=405	37-38 weeks GA % N=1949	p[a]	<37 weeks GA aORs[b]	95% CI	37-38 weeks GA aORs[b]	95% CI
Maternal age							
<20 years	3.7	2.5	0.002	1.0	0.6-1.8	1.0	0.7-1.4
20-24 years	19.1	16.2		1.1	0.8-1.5	1.1	0.9-1.3
25-29 years.	34.9	34.4		1	-	1	-
30-34 years	24.2	30.1		0.8	0.6-1.0	0.9	0.8-1.0
>=35 years	18.1	16.8		1.0	0.7-1.3	0.8	0.7-1.0
Parity							
1	48.4	40.5	0.004	1.6	1.3-2.1	0.9	0.8-1.0
2-3	40.8	51.1		1	-	1	
4	10.8	8.3		1.3	0.9-1.9	1.2	1.0-1.4
Previous preterm birth							
No	84.6	94.5	<0.001	1	-	1	-
Yes	15.4	5.5		9.3	6.6-13.0	2.4	1.9-3.1
Maternal height							
Q1: 100-160 cm	38.2	33.0	<0.001	1.4	1.1-1.9	1.3	1.1-1.5
Q2: 161-165 cm	26.4	30.1		1.0	0.8-1.4	1.2	1.0-1.4
Q3: 166-168 cm	14.5	15.7		0.9	0.6-1.3	1.0	0.9-1.2
Q4: 169-190 cm	21.0	21.1		1	-	1	-
Pre-pregnancy BMI							
<18.5	15.3	10.4	<0.001	1.9	1.4-2.6	1.3	1.1-1.5
18.5-24.9	61.9	67.1		1	-	1	-
25-29.9	13.6	14.7		0.8	0.6-1.0	0.8	0.7-0.9
>=30	9.3	7.8		0.9	0.6-1.3	0.7	0.6-0.9
Nationality							
French	83.7	87.1	0.6213	1	-	1	-
Other Europe	5.4	3.7		1.5	1.0-2.5	1.1	0.8-1.4
North African	5.7	3.9		1.2	0.8-2.0	0.8	0.6-1.0
sub-Saharan Africa	3.1	2.5		1.2	0.7-2.3	1.0	0.7-1.4
Other	2.1	2.8		0.8	0.4-1.7	1.1	0.8-1.5
Level of education							
Low ISCED 0-2	37.1	30.4	<0.001	1.4	1.0-1.9	1.1	0.9-1.3
Medium ISCED 3-5	38.4	39.7		1.1	0.8-1.4	1.0	0.9-1.1
High ISCED 6+	24.5	30.0		1	-	1	-
Smoking n° cigarettes/day during the 3rd trimester							
0	78.0	82.2	<0.001	1	-	1	-
1-9	13.5	11.9		1.0	0.7-1.3	0.9	0.8-1.1
>=10	8.5	5.9		1.5	1.0-2.2	1.2	0.9-1.5

a. F-test b. Adjusted Relative Risk Ratio

In Table 3, we display the associations between indicated preterm and early term birth by maternal characteristics. Out of all births, 2.6% were indicated preterm deliveries and 8.8% were indicated early term deliveries. Most risk factors were common to indicated preterm and early term birth including: advanced maternal age, a previous preterm birth, short stature, BMI over 30, sub-Saharan African origin (aOR 2.2[1.4-3.5] preterm, and aOR 1.6[1.2-2.2] for early term), and a low level of education, after adjusting on all other covariates. Primipara were only at risk for indicated preterm birth, aOR=2.1[1.6-2.7]; while parity 4+ was associated with greater odds of indicated early term birth aOR= 1.3 [1.1-1.6].

Table 3: Associations between maternal characteristics and risks of indicated preterm and early term birth

	<37 weeks GA % N=374	37-38 weeks GA % N=1259	p[a]	<37 weeks GA aORs[b]	95% CI	37-38 weeks GA aORs[b]	95% CI
Maternal age							
<20 yo	4.1	1.9	0.0000	1.1	0.6-2.0	0.9	0.6-1.4
20-24 yo	13.5	11.9		0.8	0.6-1.1	0.9	0.8-1.2
25-29 yo.	30.5	27.6		1	-	1	-
30-34 yo	31.6	30.1		1.3	1.0-1.7	1.2	1.0-1.4
>=35 yo	20.3	28.4		1.4	1.0-1.9	1.8	1.5-2.1
Parity							
1	51.5	36.6	0.0000	2.1	1.6-2.7	1.0	0.9-1.2
2-3	38.8	50.3		1	-	1	-
4	9.7	13.2		1.1	0.7-1.6	1.3	1.1-1.6
Previous preterm birth							
Yes	89.0	93.5	0.0000	6.6	4.5-9.7	2.5	1.9-3.3
No	11.0	6.5		1	-	1	-
Maternal height							
Q1: 100-160 cm	37.2	36.9	0.0000	1.3	1.0-1.8	1.5	1.3-1.8
Q2: 161-165 cm	25.2	29.3		1.0	0.7-1.3	1.2	1.0-1.5
Q3: 166-168 cm	15.9	14.4		1.0	0.7-1.4	1.0	0.8-1.3
Q4: 169-190 cm	21.6	19.3		1	-	1	-
Pre-pregnancy BMI							
<18.5	10.4	5.6	0.0000	1.4	1.0-2.1	0.8	0.6-1.1
18.5-24.9	57.7	58.3		1	-	1	-
25-29.9	17.6	19.6		1.0	0.8-1.4	1.1	0.9-1.3
>=30	14.4	16.5		1.6	1.1-2.2	1.7	1.4-2.0
Nationality							
French	84.2	84.9	0.0044	1	-	1	-
Other Europe	2.9	2.8		0.8	0.4-1.6	0.8	0.6-1.2
North African	4.1	5.1		0.8	0.5-1.5	0.9	0.7-1.2
Sub-Saharan Africa	5.9	4.6		2.2	1.4-3.5	1.6	1.2-2.2
Other	2.9	2.6		1.2	0.6-2.2	1.1	0.8-1.6
Level of education							
Low ISCED 0-2	38.0	34.2	0.0000	2.0	1.5-2.8	1.5	1.3-1.8
Medium ISCED 3-5	39.4	42.0		1.4	1.0-1.8	1.3	1.1-1.5
High ISCED 6+	22.7	23.8		1	-	-	1
Smoking n° cigarettes/day during the 3rd trimester							
0	80.5	80.3	0.0068	1	-	1	-
1-9	14.1	14.1		1.1	0.8-1.5	1.2	1.0-1.4
>=10	5.4	5.6		1.0	0.6-1.6	1.1	0.9-1.5

a. F-test b. Adjusted Relative Risk Ratio

Discussion

Our study provides new insight into the population determinants of preterm and early term birth by mode of onset of delivery. We identified shared risk factors for delivery before 39 weeks which were: a previous preterm birth, short stature, a low level of education, underweight (overall and in spontaneous deliveries), obesity (in indicated deliveries only), and foreign origin (for other European and sub-Saharan nationals). The impact of most risk factors was greater for preterm birth compared to early term birth, and primiparity was a risk factor for preterm birth but not early term birth.

A strength of our study is the availability of detailed information on prenatal, social and demographic characteristics collected using a standardized maternal interview in a representative sample of births in France. We had few missing data for which we corrected using multiple imputation. Nonetheless, there were some limitations. Our sample size may have been too small to detect low to moderate associations in less prevalent subgroups of women, such as heavy smokers, for instance. We also did not correct for multiple comparisons in order to maintain adequate power to carry out the study (34). Because very preterm births (births <32 weeks: n=83) represented 0.6% of births in our sample, we did not report associations by preterm GA subgroups. It is possible that risk factors for this vulnerable subpopulation may differ from those for moderate and late preterm births at 32-36 weeks of gestation. Finally, we did not have data on the complications of pregnancy associated with earlier delivery.

The strongest single predictor of both preterm and early term delivery was a previous preterm birth, as confirmed in other population-based studies (36, 119) and a recent systematic review which showed a 30% risk of recurrent spontaneous preterm birth (sPTB) following sPTB in singleton pregnancies (80) . We also found that first-time mothers were more likely to deliver preterm, but not early term. Therefore, the shape of the risk distribution for early delivery in first-time mothers may slightly differ from the overall GA distribution which peaks

around 38-40 weeks of gestation. These results indicate that within countries, fertility trends determining the proportion of primiparous women are likely to contribute to preterm and early term birth rates.

Socio-demographic characteristics were also associated with earlier delivery. Women with a lower level of education were more likely to deliver preterm and early term, confirming well known associations on education and preterm birth risk, and recent findings from Canada on the association with early term birth (8, 83). Exposures related to mothers' general quality of life and well-being (i.e. living and employment conditions, air pollution, exposure to stress) could mediate the association with social status via physiological pathways (105, 108, 110, 122). In France, Prunet et al. showed that social status was associated with preterm birth risk independently of use of medical care during pregnancy (84, 85). As for the association with foreign origin, our results are consistent with the literature showing higher risks of preterm birth among women from Sub-Saharan Africa (41).

There were common anthropometric determinants of delivery before 39 weeks overall and by mode of onset of delivery. Our findings confirm previous research on the association between preterm birth and short stature (30) (51) and we provide new evidence on the association with early term birth. With respect to maternal pre-pregnancy weight, thinness is often associated with spontaneous preterm birth but the association between GA and overweight is less clear (24) (66, 111). A greater prevalence of comorbities in obese women could contribute to the excess in indicated delivery (48), which we observed. We also found a decreased risk of spontaneous preterm and early term delivery in women with BMIs over 30 which could be due to specific delivery practices, and greater levels of obstetrical interventions for obese women in general(53).

Finally, smoking and advanced maternal age are traditionally cited as preterm birth risk factors (29); while there was an increased risk for spontaneous preterm birth in heavy smokers and an increased risk for indicated preterm and early term delivery in mothers over 35, we did not identify associations with either variable in the overall analyses. Previous data from France, also showed a limited impact of smoking on overall preterm birth risk whereas associations were stronger in studies from other countries (18, 84).

Our findings showing common risk patterns for preterm and early term births suggest a shared etiology for these births overall, with some exceptions for primiparous women and by mode of onset of delivery. These results are consistent with two reports documenting shared pregnancy complications for spontaneous preterm and early term deliveries (22), but a more heterogeneous etiology for medically indicated late preterm and early term delivery (i.e. chronic medical conditions like anemia and gastrointestinal disease were associated with late preterm but not early term delivery) (20). Future research associating maternal exposures with pregnancy complications such as: diabetes mellitus, infection and inflammation, placental ischemia, polyhydramnios and oligohydramnios, which are related to spontaneous and indicated preterm and early term births could provide insight into the mechanisms underpinning early delivery.

In conclusion, our population-based study showed that there are shared maternal prenatal and socio-demographic risk factors for delivery before full term (i.e. 39 weeks and over). Because strategies to reduce individual risk of preterm birth have had a limited impact on global rate reductions (22), investing in broader population-based interventions may be justified, including those targeting maternal pre-pregnancy BMI and social inequalities in health (48). Moreover, due to the large volume of births at 37-38 weeks, even small point percentage reductions are likely to impact on health and needs for educational and social services. Each additional week of gestation after 35 weeks reduces specific delays in

communication, personal-social, fine-motor, and problem-solving skills up until 24 months of age, and the population attributable fraction for poor achievement in school is highest among early term births (31, 97). The existence of shared risk factors for both gestational age subgroups and the greater number of early term births compared to preterm births provides greater power to investigate the mechanisms leading to early delivery, and supports the use of a broader research paradigm for preterm birth prevention.

Contributions: MD, BB and JZ contributed to the study design, and interpretation of the data. MD, BB, and CP participated in the data collection and analysis. MD and JZ drafted the manuscript, BB provided critical revisions. All authors have read and approved the final version of the manuscript.

Data sharing statement: Instructions for applying for public access data from the French National Perinatal Survey are available upon request from the authors.

Chapter 7: Summary and final discussion

Identifying sources of variability in preterm birth rates between countries can provide relevant information for designing policies to mitigate these differences and contribute to effective preterm birth prevention (103, 120). In this final chapter, we summarize our main findings and highlight the implications of our work within the broader context of international research and surveillance.

1. Synthesis

Main Findings

There were wide preterm and early term birth rate differences across countries across 34 high income countries. Singleton live preterm birth rates ranged between 5% and 10 % in 2010, while very preterm birth rates (22-31weeks) ranged between lows of 6‰ and highs of 16‰ in 2010. Early term birth rates also varied two-fold, ranging between 15% and 30% across countries. In our literature review, we identified the most likely sources of rate variations across high-income countries which share similar levels of development and access to medical knowledge, and assessed current research on how these factors affect variability across countries and time. We identified multiple exposures including BMI, smoking, and environmental factors as well as health system factors such as practices related to indicated preterm deliveries, which determine preterm birth risk and could play a role in explaining cross-country variations. We also found it important to clarify the potential contribution of artefactual differences owing to measurement, as these have been found to contribute to differences in perinatal health indicators across European countries.

We assessed the feasibility of using national health information systems to compare preterm birth rates and showed that PTB rankings were related to differences in reporting

practices for births and deaths across perinatal data systems. Comparing the proportion of periviable births (22-23 weeks) and stillbirths among very preterm births across countries highlighted where there might be less reliable data at early gestational ages. Based on these results, we recommend excluding births at 22-23 weeks of gestation and TOP from international VPT comparisons using routine data sources. Analyses in Chapter 4, which included countries with similar reporting criteria and complete coverage of births, led us to conclude that there were true differences in preterm birth rates overall and by other GA subgroups.

We also provided novel insights into the variation in preterm birth rates and trends by showing that these reflect broader shifts in the GA distribution towards early delivery, as detailed in Chapter 5. Countries with high late and moderate preterm birth rates were more likely to have early term birth rates and lower mean term GA. Early term birth rates and preterm birth were correlated overall and for indicated and spontaneous births. Of note, rates for very preterm births were not associated with other GA subgroup rates which could indicate different causal pathways leading to delivery at the extremes of gestation. Our results showing strong correlations between preterm and early term birth rates and trends suggest a shared etiology for these early deliveries. As early term birth provide greater numbers to investigate population exposures that may have small impact at the individual level (i.e. smoking or maternal age), adopting a broader paradigm may therefore be an interesting approach for future studies.

In line with the premise raised by these cross-national findings, our analyses of individual data from France in Chapter 6 showed that most PTB risk factors were common to preterm and early term birth, including a previous preterm birth, short stature, a low level of education, underweight, obesity and foreign origin. The modifiable population determinants of delivery before 39 weeks, more specifically, the level of education and BMI could constitute promising targets for PTB and ETB rate reductions in France (48). However, there are some

key differences in risk factors to take into account, including primiparity, and BMI which differed by mode of onset of delivery.

In summary, our doctoral work identified a range of potential population exposures that impact on the preterm birth rate (cf. Chapter 2). Our analyses contribute to the discussion of data items useful for a better estimate of prematurity (cf. Chapter 4) and the methods that can be used in comparative analyses using international GA data (cf. Chapter 5). This work could be used to better tailor the objectives of national PTB programs and evaluate them according to common criteria across countries. We also provide insight into the determinants of early delivery before full term, and suggest that investing in population-based PTB prevention interventions (i.e. that target all births before 39 weeks) could be a worthwhile public health strategy given the larger numbers of early term births which could also be avoided.

Strengths and limitations

We had access to routine aggregate data from 34 countries over a 12 year period: in 1996, 2000, 2004, 2008, 2010, using a common protocol. We also had detailed information on mothers' social and demographic characteristics in France; there were few missing data, for which we corrected using multiple imputation. The Euro-Peristat and PREBIC projects provided a platform of researchers, statisticians and clinicians which allowed us to collect these data as well as disseminate our findings to national experts on prematurity and perinatal health surveillance. These key players provided a more detailed perspective on the clinical and public health aspects of countries.

However, there were some limitations. We requested data using the best obstetric estimate of gestational age, albeit ultrasound is routine in most countries, we had no further information on how that estimate was derived. In addition, previous Euro-Peristat studies suggested that the recording of mode of onset of delivery is not always comparable in

international data systems because of how induction is measured (i.e. inclusion of artificial rupture of membranes (or not), unclear distinction between induction rather than augmentation of labour, and how provider indicated caesareans are recorded (elective vs. emergency caesareans, or caesareans before or after onset of labour). This complicates the interpretation of data on indicated preterm births across countries, although definitions in routine systems are unlikely to change and trends by mode of onset of delivery are therefore more robust. Some countries did not have these data recorded in their routine systems (i.e. 16 countries out of 34 in 2008 – cf. Chapter 4).

Finally our data were aggregated in Chapters 4-5, and we were unable to stratify by other factors that may affect the preterm birth rate. Hence, we conducted ecological analyses and within country variations could not be explored. In Chapter 6, our sample size may have been too small to detect low to moderate associations in the least prevalent groups of women (i.e. heavy smokers). Also, very preterm births (n=83) represented 0.6% of births in our sample and we did not report associations by preterm GA subgroups (i.e. <32 for very preterm, 32-36 moderate and late preterm births), even though risk factors for this vulnerable subpopulation are likely to differ.

2. Improving international perinatal health statistics by adding indicators of preterm birth

Health indicators are used to monitor the health and well-being of populations and to measure health systems' performance. Indicators describe outcomes, measure the efficacy and breadth of interventions, and point out gaps in coverage. They are used to inform evidence based medicine and policy making. When integrated in routine data collection exercise, they provide relevant and comparable information on trends in time. High-quality data on clinically

relevant subcategories are also needed by health care professionals and planners to evaluate practices for higher risk and lower risk infants, as well as to monitor more effectively the uptake of prevention policies.

PTB Prevention programs need valid benchmarks to compare and evaluate their interventions, but preterm birth is not an indicator available in international statistical systems. In high-income countries, most preterm infants, that is the moderate and late preterm births, weigh at least 2500 g (57) and traditionally, low birth weight has been used instead of GA as a perinatal and public health intervention marker (62, 117). Nonetheless, the relevance of using BW over high-quality GA data is debated (25, 57, 117). Wilcox et al. showed that when comparing two populations, the only difference in birthweight that directly affects mortality is the difference in the rate of small preterm births, meaning that the range of outcomes genuinely associated with birth weight may be narrower than originally described (13).

One of our aims for this thesis was to overcome artefactual biases and determine the methods which should be used for a better estimate of preterm birth. Only recently, did Eurostat start to collect data on live births by birthweight and duration of gestation. GA data for Eurostat are provided by Member States on a voluntary basis and were available from 9 countries in 2015. Our findings using the Euro-Peristat and PREBIC datasources demonstrate the feasibility of collecting preterm birth data from 34 countries using a standardized protocol. Possible difficulties in comparing PTB data at the extremes of gestation may arise but are unlikely to affect rates for all preterm births under 37 weeks.

Another key message from our research is to encourage countries to improve and standardise reporting of births at the extremes of gestation. GA is a criteria for practice and resuscitation practice with strong implications for health resources allocation. Advances in neonatal medicine over the past decade have pushed back the limits of viability and an

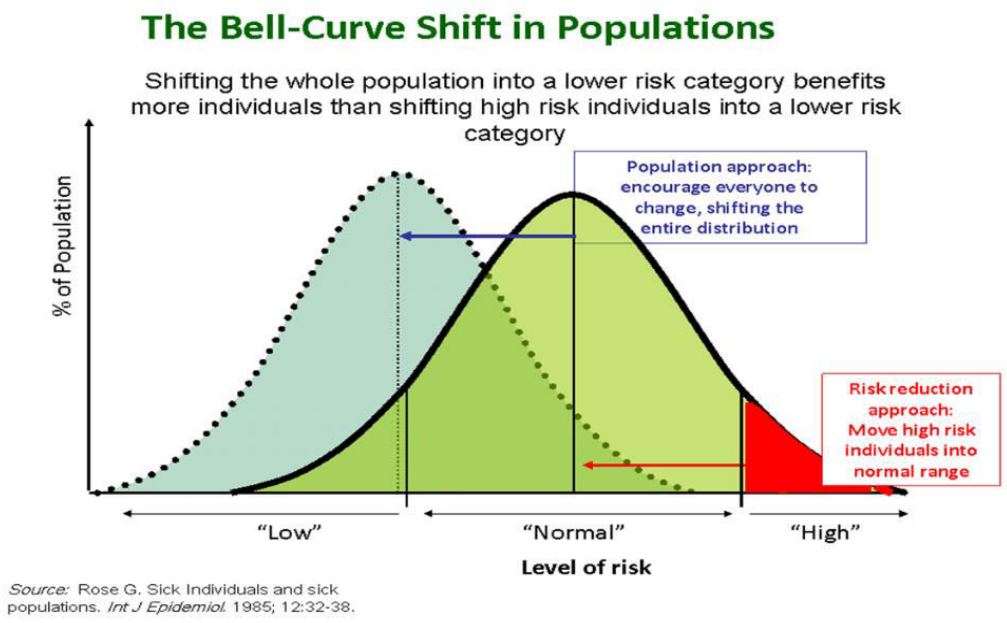
increasing number of these births are being resuscitated (2,3). In addition, although there are relatively few births at 22-23 weeks, they disproportionately contribute to the overall burden of perinatal mortality. In this context having high quality international data on periviable births and stillbirths is particularly important. A lower GA threshold warrants the most comprehensive reporting on the full spectrum of maternal and child health birth outcomes. GA data must also be collected by completed week to allow stratification and computation of comparable indicators. Other data on contextual factors such as population characteristics, and health service use are also needed to interpret preterm birth rate variations and trends; the Euro-Peristat project provides these perinatal indicators for Europe.

In 2012, the WHO released the Born Too Soon series, a global call for action on preterm birth prevention. Experts from over 50 regional, national and international organizations urged to implement consistent recording of all pregnancy outcomes, including stillbirths, and standard application of preterm definitions to advance the understanding and the surveillance of preterm birth rates and trends(16). High-income countries have the means to improve international perinatal health statistics by adding indicators of preterm birth. Differences in population risk factors over time highlight the importance of routine perinatal health surveillance for prevention when women's behaviors and medical practices are subject to change (84). We are hopeful that in the future, results from international comparative analyses will encourage national agencies to improve the information available on births at the earliest GAs, allowing for the best use of data collected on preterm birth.

3. Broadening the scope of preterm birth prevention for a greater public health impact

In the last decades, the focus in high-income countries has been on the management of the consequences of prematurity more than on prevention (22, 99), reflecting limited achievements in preventing preterm birth case incidence compared with the medical advances that have reduced mortality. Two types of approaches guide policies aimed at reducing disease incidence. A first, known as *high-risk reduction*, seeks to reduce the exposure in the small number of individuals the most at risk. A second approach is *population-based*, and aims to reduce the average risk on all people (cf. Figure 2) (90).

Figure 2. The Bell-Curve Shift in Populations



PTB diagnostic procedures today essentially target a selected subset of high-risk pregnancies (22), such as transvaginal ultrasound screening for a shortened cervix or vaginal fetal fibronectin assessments. However such interventions have low predictive accuracy and bear high costs for the health care system (43, 44). Chang et al. showed that the potential impact

of current prevention strategies in high-income countries was limited to an estimated -5% rate reduction (22). We need to do better. Our doctoral work shows that given the shared risk factors for preterm and early term birth, honing in on the more subtle population determinants of earlier delivery could be one way to rethink current research and policy approaches. However, our work also suggests that for many PTB population risk factors, the mechanisms through which these determinants explain differences across countries have not been evaluated.

A population approach for preterm birth prevention is not a new paradigm. In the late 70's, in the Hagenau region in France, Papiernik et.al implemented a successful intervention. The program took place from 1971-1982 and was aimed at all risk groups, as opposed to a high-risk intervention which would have targeted only women with a previous stillbirth or teenage pregnancies. Despite an overall PTB increase from 5.6% in 1981 to 6.2% in 1998 due to a rising number of multiple births, the singleton live birth rate decreased by one third overall from 7.9% in 1972 to 4.0% in 1989, and rates for births less than 34 weeks of gestation decreased by one half from 1.1% (1971–1974) to 0.5% over the study period (1979–1982) (78). The initial success of the program in the Hagenau region over the period 1971-1982, led to an expanded nationwide intervention in the 1980's. The intervention included specific prenatal care interventions for all, within a broader context of greater social protection for working pregnant women (54). Of note, acceptance of the programe varied by maternal level of education (79). Results from the Hagenau experience showed the intervention had no preventive effect on *high-risk* women: women with a previous preterm birth, previous stillbirth, women with a bleeding episode during the second or third trimester, women younger than 20 years or older than 36 years. However, the intervention had the greatest impact for women in the low-risk majority.

The Hagenau experience illustrates that the effectiveness of their population approach resided in improving the well-being and health of the majority of women. Births before 39 weeks represent between 20 and 40% of all births. Because there are common population

determinants for these births as well as common biological determinants (21), efforts to reduce early term births are likely to benefit preterm birth prevention as well. Targeting the shared population determinants of early delivery <39 weeks could help steer a greater number of births towards lower levels of risk.

Early term births are an interesting target for broad public health interventions (1, 5). These infants are susceptible to adverse outcomes across various sectors of health and well-being and throughout the lifecourse, although these risks are less acute than for preterm births. Due to the large number of births at 37-38 weeks, even small point percentage reductions could potentially have a wide reach on key population indicators of health status and service use (including in education, and social care). For example, research shows that each additional week of gestation after 35 weeks predicts specific delays in communication, personal-social, fine-motor skills, and problem-solving up until 24 months of age (31). In Australia, the population attributable fraction for poor achievement in school is highest among early term births (97).

Preterm birth is widely recognized as a syndrome with multiple etiologies (11, 47); and exploring the associations between social determinants and pathological mechanisms is an important area for research. Papiernik et al. believed the differences between the high US rates and the lower European rates could be explained by the European social health policy model and better protection of pregnant women and their newborns (78). However, even within Europe, maternity leave policies vary across Member States. The current EU legislation calls for 14 weeks minimum of paid work leave in the period immediately preceding and following delivery, of which 2 weeks are mandatory. The number of weeks vary from a total of 10 weeks in Portugal for prenatal and postnatal leave to 58 weeks in Bulgaria. Payment also varies from 65-70% paid leave in Slovakia, the Czech Republic, Hungary and Cyprus to 100% in other EU MS (101). At the individual level, the EUROPOP study conducted in 2004 in 16 European countries showed that specific working conditions: “working more than 42 hours a week (OR

= 1.33, CI = 1.1 to 1.6), standing more than six hours a day (OR = 1.26, CI = 1.1 to 1.5), low job satisfaction (OR = 1.27, CI = 1.1 to 1.5), were related to preterm birth risk." Associations were strongest in countries with a lower overall level of perinatal health and a common practice of long prenatal leaves (95).

More generally, to address determinants for health that are influenced by factors outside of the direct scope of the health, national and international stakeholders from different sectors: policy, education, employment and social care will have to work together on a more equitable health care system, and focus on the added value that health promotion and prevention can bring. While high-risk interventions are necessary to address the pathological determinants of early delivery, health policy planners might have to incorporate wider social aspects in their negotiations to target the overall population of pregnant women and provide the delivery of high quality universal care. Immediate priorities for prevention require countries to think about what types of interventions are made available at the local, regional and national level, and what resources are invested in evaluating complex cross-sectoral interventions and policies. By investigating earlier delivery as an outcome, as opposed to preterm delivery only, it may be easier to evaluate the impact of these interventions.

Finally, precision public health is an emerging concept which may provide innovative targets for population PTB prevention. The concept is derived from the field of precision medicine which aims to target "the right population at the right time for the right treatment". With this approach, the explicit objectives are to harness and integrate the massive amounts of data generated from multiple sources on epidemiological, social and obstetric factors which contribute to PTB risk, and that might not be available otherwise in patient records or routine registers (75). Newnhan et al. propose to reinforce primary screening for PTB risk factors through the use of "Omic" technologies, and also to exploit the development of Geographic information systems, mobile sensor technologies, e-registries and web-based surveillance

systems. With respect to a population framework, big data may constitute a new opportunity to fine tune interventions by linking databases and enriching existent data on mothers' lifestyles and the distribution of environmental teratogens (75). Although for this, it is crucial to consider the acceptability and data privacy issues for parents and health care providers.

4. Provider-initiated preterm births

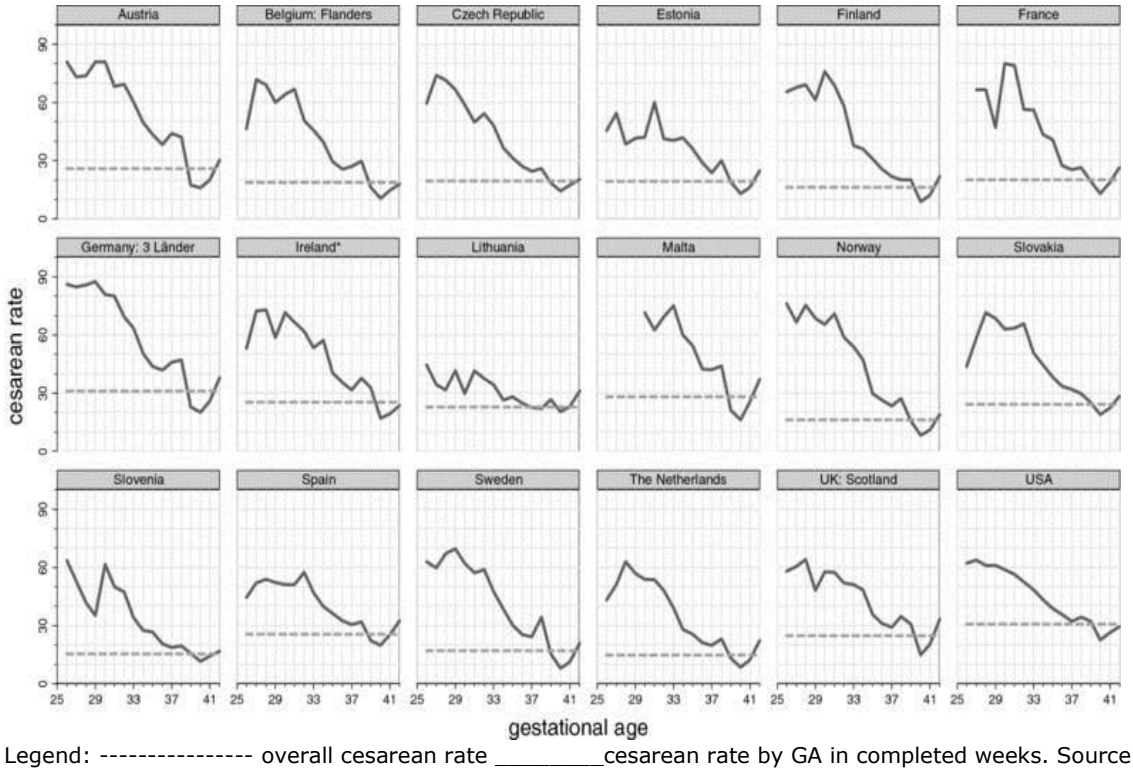
Late preterm births represent 70% of all preterm births (16). Some postulate that the most feasible approach to rapidly lowering the overall rate of preterm birth is to address indicated preterm deliveries(74). This requires a better understanding of the etiology of indicated late preterm birth on one hand, as well as the mechanisms through which national obstetrical practices relate to preterm delivery risk. For this thesis, we conducted analyses for provider-initiated and spontaneous births separately, despite differences in the definitions that are used across countries for mode of onset of delivery (as indicated in our limitations).

We found that the mechanisms underpinning shifts in the GA distribution for spontaneous and provider initiated births were on the whole similar across 34 countries using aggregate data (cf. Chapter 5), and in France after adjusting for socio-demographic confounders like maternal age, parity, and obstetric history (e.g. a previous preterm birth) (cf. Chapter 6). Most likely, these results reflect the contribution of deliveries for which they are common underlying pathological causes which lead to early parturition, or require early delivery if the mother or child's health is at stake. However, in supplementary aggregated analyses we found that risk factors for spontaneous preterm and indicated preterm delivery were not interchangeable: changes in indicated preterm deliveries were not significantly correlated with changes in spontaneous early term deliveries (adj-Pearson's $r=0.11$, $p> 0.05$, $N=42$), nor were changes in spontaneous preterm deliveries significantly correlated with changes in indicated early term

deliveries (adj-Pearsons' r= -0.32, p>0.05, N=42). These results may relate to a more heterogeneous proportion of non-medically indicated deliveries across countries.

In preliminary analyses to this doctoral work, we had investigated differences in mode of delivery for multiples and singletons in 17 European countries and the United States (28). There were large differences in countries' rates of obstetric interventions overall and in each week of gestation. In singletons, rates were highest for very preterm births and declined to a nadir at 40 weeks of gestation, but patterns differed across countries throughout the GA continuum and for multiples as well (cf. Figure 3). Studies that have analyzed underlying differences in women's risk profiles found that significant variations in cesarean use between countries or regions of a same country remained after risk adjustment (10, 65, 123). Cesarean section rate differences by GA highlight areas where consensus on best practices is lacking and could be used in developing evidence based recommendations to reduce non-medically indicated preterm deliveries.

Figure 3. Cesarean rates for singleton births overall and by GA at delivery in 2008



Legend: ---------- overall cesarean rate _____cesarean rate by GA in completed weeks. Source: (28)

Although delivery may be induced due to concerns with the health of the fetus and the increased risk of stillbirth, the evidence for these interventions is not always conclusive on the benefits to the child of early delivery (28). For example, Malloy et al. and Offerman et al. found that in preterm infants 32-36 weeks, caesarean section increased the risk of neonatal mortality and morbidity (69, 77). On the other hand, in an Australian population-based study, Bergenhenegouwen et al. found that in women delivering a breech fetus, preterm cesarean delivery was associated with reduced perinatal mortality and morbidity (14). And in a study by Ananth et al. increasing rates of preterm cesarean in the US from 1990-2004 were associated with improved perinatal survival, essentially due to considerable declines in stillbirths (7). The lack of consensus on the benefits of obstetrical intervention in preterm deliveries suggests that some of these provider-initiated deliveries may be amenable to GA-specific rate reductions. In other terms, preterm birth prevention may benefit from more targeted cesarean reduction policies and from quality assurance programe aiming to prevent iatrogenic interventions.

Current efforts to reduce elective deliveries are concentrated in the United States and focus on non-medically indicated births before 39 weeks, in part because of the high proportion of early term births in the US (~30%). Recommendations to decrease provider-initiated deliveries interventions (either labor induction or prelabor cesarean delivery) have been linked to decreases in late preterm and early term birth (87) with no concurrent increase in stillbirth rates(23), and the increased rate of prematurity has also been linked to the number of performed labor inductions (125).

In conclusion, a population approach implies that overall PTB rate reductions could be achieved by targeting the low-risk majority, but the greatest relative rate reductions may be possible in subgroups which demonstrate the highest variability. This discussion is also relevant to the choice of outcome measures for PTB prevention programs, as we saw rising overall PTB

rates and clinical subgroups trends can diverge (i.e. singleton vs multiples, or indicated vs. spontaneous preterm births)(78, 124).

5. Conclusion

There are wide differences in very preterm, moderate and late preterm, and early term birth rates among countries with comparable health systems performance, and similar inclusion criteria, and complete coverage of all births. Differences in these rates have wide-reaching implications for public health. Besides their impact on national perinatal mortality rates (37, 38, 67), the health and financial burden of neurodevelopmental impairment is very high among preterm survivors (59, 70, 94, 96). The wide range of rates observed in countries with similar levels of development suggests that potentially modifiable population or health care factors and practices, merit further study.

Medical advances have improved outcomes for infants born before term but, preterm birth prevention, defined as effective medical interventions supported by policy initiatives aimed at the general population constitutes a continued scientific and public health challenge (12, 55). Regularly reported international data on the gestational age distribution are needed to provide country-specific benchmarks for preterm birth prevention initiatives, to inform decision-making and to target future investments in health care and research (71, 81). Preterm birth data are not available in routine international statistics but we demonstrated the feasibility of using population based routine data systems, and the importance of adopting a standardised approach for these comparisons.

Because current strategies to reduce individual risk of preterm birth have had a limited impact on global rate reductions (22), investing in broader population-based interventions may be justified (48). Our results suggest that a more general focus on identifying and implementing

interventions to target modifiable population-level risk factors for early delivery in research, clinical practice, and health policy may provide a useful prevention paradigm.

Monitoring of preterm birth at the international level carries implications for evidence-based medicine and health policy making. Case study results from France highlight the impact of the socioeconomic determinants of health, and warrant accrued vigilance to the needs of women from Sub-Saharan Africa. Furthermore, addressing the more subtle determinants of early delivery such as: women's level of education or BMI, may reconcile current high-risk clinical approaches within a larger public health promotion framework policy. Moreover, practices and policies in link with induced preterm births and assisted reproductive technologies impact on overall PTB. Preterm birth as a marker of perinatal health systems performance, could help assess changes in practice for subgroups at higher risk of adverse outcomes namely preterm, early term deliveries and multiple births.

The prevention of early delivery calls for broad comprehensive and cross-sectoral interventions even outside the health sector. A first step is to consider PTB prevention as a tangible policy outcome of investments in the maternal and perinatal health sector at large. A better integration of maternal and child health concerns to local and national health impact assessments, could be an important objective for preterm birth prevention. For example, a recent study estimated that nearly 3 million preterm births may be associated with fine particulate matter ($PM_{2.5}$) exposure in 2010 globally (68). Progress will also depend on advances in basic research, since exposures which drive GA subgroup rate variations are directly related to physiological mechanisms which have yet to be precisely identified.

6. Perspectives

Reducing prematurity is an integral part of the Millennium Development Goals, and is intrinsically related to objectives to reduce infant mortality. International comparisons are a learning opportunity for countries to improve delivery of health care services and policies to raise the status of women and babies' health. Whereas diagnostic tools have failed clinicians in predicting preterm birth risk, addressing the broader determinants of preterm birth requires intersectoral action and governance for health. Major public health issues, such as preterm birth prevention, are defined by targets related to population characteristics, organization and access to care, and public health policies at national and international level. We highlighted potential synergies across public health initiatives to decrease the medicalization of childbirth and the burden of preterm delivery (15)

Greater coherence in preterm birth prevention targets can be achieved by bridging across public policy areas, and the sectors of research and population statistics. Our work on a better estimate of preterm birth for international comparisons could contribute to updates in the perinatal health items of the European Core Health Indicators (ECHI). The ECHI data collection exercise stems from a long-term collaboration between the EU Member States and the European Commission which aims to create a comparable health information and knowledge system to monitor health at EU level. The ECHI project is updating their indicators and the Euro-Peristat project has been invited to contribute their recommendations for perinatal health monitoring.

At the European level, the methodology we used to identify population factors which shift the GA distribution towards earlier delivery in France could be applied in other high-income settings, as we have validated our analytical framework in 34 countries. Furthermore, our research could be relevant to inform global public health policies in low development index countries where perinatal mortality rates are high and rates of obstetric interventions are rising, but national data on prematurity are often missing and are needed for shaping future policy.

In conclusion, we need to make sure that there is strong commitment for preterm birth prevention among all key stakeholders at both the EU and the national level supported by high-quality measurement indicators. As programs derive benchmarks for preterm birth prevention, inconsistencies in health performance do not necessarily stem from a lack of evidence, but can highlight the difficulties with implementing change when health recommendations conflict with industrial interests, personal life style choices and behaviors, or even cultural norms and practitioner attitudes. Civil society and perinatal health organizations also have a role to play in drawing attention to some of the roadblocks to preterm birth prevention, and increased capacity for comparative research analyses will further preterm birth prevention efforts. Collaborations with professional organisations and user groups could provide significant leverage to bring out the importance of these data, and advocate for the uptake of evidence-based recommendations within national perinatal health networks.

Annex

Appendix A. Routine data sources on the distribution of gestational age in 1996–2010

Country	Data source/Institution	Study years GA data	Study years Mode of onset of labor	Type of data
				P: Population H= Hospital O= Other
Austria	Birth statistics	2008, 2010	NA	P
Australia: New South Wales	New South Wales (NSW) Perinatal Data Collection (PDC)/ Centre for Epidemiology and Research. Sydney: NSW Ministry of Health	1996, 2000, 2004, 2008,2010	1996, 2000, 2004, 2008	P
Belgium: Brussels	Centre d'Epidémiologie Périnatale (CEpiP)	2004,2010		P
Belgium: Flanders	Study Center for Perinatal Epidemiology (SPE)	1996, 2000, 2004, 2008, 2010	1996,2000, 2004, 2008	H
Belgium: Wallonia	Centre d'Epidémiologie Périnatale (CEpiP)	2004,2010		P
Canada	Discharge Abstract Database, Canadian Institute for Health Information (CIHI)	2005,2008,2010	2005,2008	H
Czech Republic	Institute for Health Statistics and Information of the Czech Republic (UZIS CR)	2008,2010	2008	P
Denmark	The Medical Birth Register	2004,2010	NA	P
Estonia	Estonian Medical Birth Register	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	H

Finland	Medical Birth Register	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	P
France	French National Perinatal Survey	1995,1998,2003, 2010	1995,1998, 2003	P
Germany: National	AQUA_German Perinatal Register	2004,2010	NA	H
Germany: Hesse	Hesse Regional Institute of Quality Assurance, GQH,	2000,2004,2008	2000,2004, 2008	P
Germany: Bavaria	Bavarian Regional Institute for Quality Assurance, BAQ, Munich	2000,2004,2008	2000,2004, 2008	P
Germany: Lower Saxony	Lower Saxony Regional Institute of Quality Assurance, ZQ, Hanover	2000,2004,2008	2000,2004, 2008	P
Iceland	Medical Birth	2010	NA	P
Ireland	National Perinatal Reporting System (NPRS)	2000,2004,2008,2010	NA	P
Italy	Birth certificates	2004,2010	NA	P
Japan	Vital Statistics Japan	1996,2000,2004, 2008,2010	NA	P
Latvia	Medical Birth Register	2004,2010	NA	P
Lithuania	Medical Date of Births	1996,2000,2004, 2008,2010	1996,2000, 2004,2008	H
Luxembourg	Perinatal Health Monitoring System	2004,2010	NA	O
Malta	National Obstetrics Information System	2000,2004,2008, 2010	2000,2004, 2008	P
Norway	Medical Birth Register of Norway	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	P
Poland	Central Statistical Office	1996,2000,2004, 2008,2010	NA	P
Portugal	National Statistics , Live births and fetal, neonatal and infant deaths	1996,2000,2004, 2008,2010	NA	P

Romania	National Institute for Statistics demographic statistics for births	2010	NA	H
Slovakia	National Health Information Center 2010	1996,2000,2004, 2008,2010	NA	P
Slovenia	National Perinatal Information System of Slovenia	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	H
Spain	National Institute for Statistics (INE)	1996,2000,2004, 2008,2010	NA	P
Sweden	Medical Birth Register	1996,2000,2004, 2009,2010	1996,2000, 2004, 2008	P
Switzerland	BEVNAT, statistics of natural population change (vital statistics)	2010	NA	P
The Netherlands	Netherlands Perinatal Register PRN	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	P
United Kingdom: England and Wales	Civil Registration of births and deaths linked to NHS Numbers for Babies records	2005,2010	NA	p
United Kingdom: Northern Ireland	Child Health System	2004,2010	NA	P
United Kingdom: Scotland	Scottish Morbidity Record (SMR02)	1996,2000,2004, 2008,2010	1996,2000, 2004, 2008	H
United States	U.S. Vital Statistics, Natality Public Use Files NCHS of the U.S. Centers for Disease Control and Prevention.	1996,2000, 2004,2008,2010	1996,2000, 2004, 2008	P

Note: (1) GA data from Austria in 1996,2004 were excluded owing to a reporting error that was corrected in 2008 and 2010, as well as data from the Czech Republic in 2000 and 2004; mode of onset of delivery data were excluded in 2008 in Slovakia.(2) Data from Canada do not include births in the Province of Québec. (3)In the US, births from California were excluded due to non-reporting of clinical estimates of gestational age before 2007.

Appendix B. 1) Distribution of gestational age for singleton live births in 1996-2010 and 2) Annual growth rates for preterm (PTB) and early term (ETB) births between 1996 and 2010

Appendix B1. Distribution of gestational age for singleton live births in 1996-2010

Country code[1]	Year[2]	VPT: %24-31 weeks GA	LPT: % 32-36 weeks GA	PTB: % <37 weeks GA	ETB: %37-38 weeks GA	MEAN GA at term (37-41 weeks GA)
be_fl	1996	0.53	4.71	5.25	23.04	39.28
es	1996	0.85	3.99	4.86	16.36	39.57
fi	1996	0.58	3.87	4.49	18.24	39.53
fr	1996	0.50	3.99	4.52	22.63	39.33
ja	1996	0.48	3.79	4.29	26.81	39.17
li	1996	0.81	3.69	4.53	13.34	39.65
ne	1996	0.70	5.41	6.15	20.91	39.46
no	1996	0.80	4.45	5.31	13.55	39.83
nsw	1996	0.67	4.52	5.23	19.72	39.48
po	1996	1.03	4.97	6.05	16.95	39.61
pt	1996	0.78	5.33	6.11	NA	NA
sa	1996	0.68	3.71	4.40	13.87	39.63
se	1996	0.61	4.16	4.78	15.70	39.52
sp	1996	0.61	5.59	6.20	17.53	39.52
sw	1996	0.68	4.27	4.97	18.09	39.58
uk_sco	1996	0.85	4.90	5.78	18.37	39.60
usa	1996	1.11	6.46	7.69	21.56	39.35
be_fl	2000	0.65	5.30	5.96	25.27	39.20
es	2000	0.93	4.06	5.05	15.43	39.59
fi	2000	0.61	4.07	4.71	17.75	39.54
fr	2000	0.47	4.22	4.69	22.75	39.33
ge	2000	0.83	6.11	6.99	22.38	39.36
ir	2000	0.70	3.71	4.45	14.88	39.73
ja	2000	0.55	3.91	4.48	27.53	39.15
li	2000	0.88	3.64	4.58	13.92	39.62
mt	2000	0.59	4.33	4.96	25.67	39.20
ne	2000	0.75	5.25	6.04	20.15	39.51
no	2000	0.84	4.56	5.44	16.39	39.66
nsw	2000	0.75	4.55	5.34	19.65	39.49
po	2000	0.89	4.62	5.54	18.07	39.56
pt	2000	0.63	4.26	4.89	NA	NA
sa	2000	0.57	3.96	4.54	15.50	39.56
se	2000	0.77	4.29	5.10	16.85	39.47
sp	2000	0.52	5.77	6.30	20.16	39.43
sw	2000	0.68	4.50	5.20	18.30	39.6
uk_sco	2000	0.93	5.11	6.08	17.99	39.59

usa	2000	1.14	6.93	8.18	24.92	39.2
be_bu	2004	0.80	4.90	5.39	20.76	39.42
be_fl	2004	0.71	5.61	6.34	25.76	39.19
ca	2004	0.84	5.64	6.57	24.46	39.28
dk	2004	0.68	4.42	5.12	19.89	39.54
es	2004	0.81	4.04	4.87	17.41	39.55
fi	2004	0.62	3.69	4.36	17.50	39.57
fr	2004	0.73	4.25	4.98	20.19	39.48
ge	2004	0.83	6.37	7.25	25.33	39.27
ge_ntl	2004	0.92	6.02	6.99	26.35	39.29
ir	2004	0.70	3.65	4.40	15.35	39.68
it	2004	0.78	4.89	5.70	25.59	39.28
ja	2004	0.55	3.97	4.54	28.59	39.12
li	2004	0.80	3.66	4.50	15.41	39.53
lu	2004	0.23	4.53	4.67	25.13	39.25
lv	2004	1.02	3.80	4.84	18.16	39.44
mt	2004	0.58	5.23	5.81	29.15	39.09
ne	2004	0.72	4.94	5.70	19.71	39.53
no	2004	0.70	4.76	5.48	18.05	39.59
nsw	2004	0.73	4.66	5.43	20.75	39.45
po	2004	0.86	4.95	5.84	20.40	39.45
pt	2004	0.46	4.75	5.42	NA	NA
sa	2004	0.71	4.49	5.21	16.55	39.52
se	2004	0.73	4.50	5.25	18.79	39.4
sp	2004	0.58	5.78	6.36	21.73	39.37
sw	2004	0.69	4.47	5.19	19.23	39.57
uk_ew	2004	1.01	5.13	6.15	18.77	39.57
uk_ni	2004	0.82	4.52	5.36	17.60	39.56
uk_sco	2004	0.96	5.28	6.28	18.05	39.59
usa	2004	1.16	7.51	8.78	28.83	39.04
au	2008	0.77	5.90	6.71	25.88	39.25
be_fl	2008	0.66	5.48	6.17	25.67	39.2
ca	2008	0.77	5.72	6.56	25.58	39.24
cz	2008	0.71	5.56	6.28	21.40	39.37
es	2008	0.72	3.85	4.63	18.16	39.53
fi	2008	0.50	3.76	4.29	16.65	39.59
ge	2008	0.83	6.14	7.03	27.31	39.22
ir	2008	0.66	3.61	4.31	15.43	39.68
ja	2008	0.55	4.10	4.68	30.23	39.07
li	2008	0.78	3.93	4.75	15.99	39.5
mt	2008	0.85	4.45	5.32	29.63	39.01
ne	2008	0.75	4.89	5.73	20.28	39.49
no	2008	0.77	4.47	5.28	18.25	39.57
nsw	2008	0.71	4.80	5.57	23.04	39.32
po	2008	0.76	4.66	5.46	20.51	39.43
pt	2008	0.79	6.62	7.41	NA	NA

sa	2008	0.83	4.78	5.62	18.74	39.44
se	2008	0.63	4.79	5.44	19.15	39.42
sp	2008	0.78	5.52	6.31	23.25	39.36
sw	2008	0.64	4.14	4.82	18.63	39.58
uk_sco	2008	0.90	5.21	6.13	16.53	39.63
usa	2008	1.13	7.34	8.57	29.72	38.98
au	2010	0.90	5.45	6.35	25.48	39.27
be_bu	2010	1.01	5.16	6.17	23.63	39.29
be_fl	2010	0.68	5.33	6.01	24.3	39.23
be_wa	2010	0.66	5.83	6.48	29.06	39.06
ca	2010	0.78	5.48	6.33	25.33	39.24
ch	2010	0.67	4.58	5.25	26.47	39.24
cz	2010	0.70	5.42	6.12	21.92	39.34
dk	2010	0.73	4.13	4.87	18.11	39.61
es	2010	0.87	3.69	4.56	17.11	39.57
fi	2010	0.54	3.80	4.34	16.06	39.61
fr	2010	0.58	4.90	5.48	22.51	39.39
ge_ntl	2010	0.95	5.51	6.46	27.35	39.27
ice	2010	0.40	3.71	4.12	15.66	39.65
ir	2010	0.71	3.52	4.23	15.56	39.66
it	2010	0.74	4.98	5.72	28.27	39.21
ja	2010	0.56	4.14	4.74	30.78	39.05
li	2010	0.73	3.58	4.32	15.69	39.50
lu	2010	0.64	5.63	6.27	29.66	39.08
lv	2010	0.95	3.96	4.91	17.47	39.43
mt	2010	0.62	4.80	5.42	30.65	39.02
ne	2010	0.83	5.02	5.86	21.84	39.41
no	2010	0.69	4.21	4.90	16.42	39.65
nsw	2010	0.70	4.72	5.48	23.40	39.30
po	2010	0.77	4.51	5.28	19.90	39.45
pt	2010	0.75	5.19	5.94	26.54	39.04
ro	2010	1.08	6.51	7.59	23.58	39.08
sa	2010	0.77	4.98	5.75	19.93	39.37
se	2010	0.78	4.71	5.49	19.09	39.42
sp	2010	0.79	5.16	5.95	22.43	39.40
sw	2010	0.65	4.09	4.74	18.30	39.58
uk_ew	2010	0.93	4.70	5.63	18.12	39.58
uk_ni	2010	0.86	4.71	5.56	16.56	39.59
uk_sco	2010	0.87	4.65	5.52	16.34	39.63
usa	2010	1.12	7.01	8.23	27.18	39.00

Notes: (1) For country codes see Table 1. “ge” refers to German data from the regions of Hesse, Lower Saxony and Bavaria in 2000, 2004, and 2008; “ge_ntl” refers to national data available in 2004 and 2010. (2) Data from Canada (ca) do not include births in the Province of Québec, and data from Australia (nsw) were limited to the region of New South Wales, which represents one-third of annual births in Australia. In the US (usa), births from California were excluded

due to non-reporting of clinical estimates of gestational age before 2007. In France (fr), data were from 1995, 1998, 2003 and 2010; in Canada (ca) and UK: England and Wales (uk_ew), from 2005 instead of 2004; and in Sweden (sw) from 2009 instead of 2008.

Appendix B2. Annual growth rates for preterm (<37 weeks) and early term (37-38 weeks) births between 1996 and 2010

Gestational age (GA) in completed weeks								
	1996 vs. 2000		2000 vs. 2004		2004 vs.2008		2008 vs 2010	
Country	PTB (% per year)	ETB (% per year)	PTB (% per year)	ETB (% per year)	PTB (% per year)	ETB (% per year)	PTB (% per year)	ETB (% per year)
Austria	-2.7	-0.8					-2.7	-0.8
Australia: New South Wales	0.5	-0.1	0.4	1.4	0.6	2.6	-0.9	0.9
BE: Brussels[1]							2.3	2.2
BE: Flanders	3.2	2.3	1.5	0.5	-0.7	-0.1	-1.2	-2.7
Canada (w/o Québec) [2]					-0.1	1.5	-1.8	-0.5
Czech Rep. [1]							-1.3	1.2
Denmark[1]							-0.9	-1.6
Estonia	1.0	-1.5	-0.9	3.1	-1.3	1.1	-0.8	-2.9
Finland	1.2	-0.7	-1.9	-0.4	-0.4	-1.2	0.6	-1.8
France[3]	1.3	0.2	1.2	-2.4			1.4	1.6
Germany			0.9	3.1	-0.8	1.9	-1.3	0.6
Ireland			-0.3	0.8	-0.5	0.1	-0.9	0.4
Italy[1]							0.1	1.7
Japan	1.1	0.7	0.3	1.0	0.7	1.4	0.6	0.9
Latvia							0.2	-0.6
Lithuania	0.3	1.1	-0.4	2.6	1.3	0.9	-4.6	-1.0
Luxembourg[1]							5.0	2.8
Malta			4	3.2	-2.2	0.4	0.9	1.7
Netherlands	-0.5	-0.9	-1.4	-0.5	0.1	0.7	1.1	3.8
Norway	0.6	4.9	0.2	2.4	-0.9	0.3	-3.7	-5.2
Poland	-2.2	1.6	1.4	3.1	-1.7	0.1	-1.7	-1.5
Portugal								

Slovakia	0.8	2.8	3.5	1.7	1.9	3.2	1.2	3.1
Slovenia	1.7	1.8	0.7	2.8	0.9	0.5	0.5	-0.2
Spain	0.4	3.6	0.2	1.9	-0.2	1.7	-2.9	-1.8
Sweden[4]	1.1	0.3	0.0	1.2	-1.5	-0.6	-1.6	-1.8
UK: England and Wales[1]							-1.8	-0.7
UK : Scotland	1.3	-0.5	0.8	0.1	-0.6	-2.2	-5.1	-0.6
UK: Northern Ireland[1]							0.6	-1.0
USA (w/o CA)	1.6	3.7	1.8	3.7	-0.6	0.8	-2.0	-4.4

Note: (1) Data in BE: Brussels, the Czech Republic, Denmark, Italy, Luxembourg and UK/ England and Wales are from 2004 and 2010 (2) Data in Canada are from 2005, 2008, 2010 (3) Data in France come from a nationally representative survey of births in 1995, 1998, 2003 and 2010 (4) 2008 data from Sweden are from 2009

Appendix C. List of contributors to the European Perinatal Health Report: Health and Care of Pregnant Women and Babies in Europe in 2010.

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List of Illustrations

(Illustrations embedded in the scientific publications are not listed here – please refer to the scientific article)

Supplementary material

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Chapter 5