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Title

Achieving orphan designation for placental insufficiency: annual incidence estimations in Europe

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On behalf of the EVERREST Consortium

Short Title: Placental insufficiency: an orphan disease

Abstract

Objective To determine whether a novel therapy for placental insufficiency could achieve orphan drug status by estimating the annual incidence of placental insufficiency, defined as an estimated fetal weight below the 10th centile in the presence of abnormal umbilical artery Doppler velocimetry, per 10,000 European Union (EU) population as part of an application for European Medicines Agency (EMA) orphan designation

Design Incidence estimation based on literature review and published national and EU statistics

Setting and Population European Union

Methods Data were drawn from published literature, including national and international guidelines, international consensus statements, cohort studies and randomised controlled trials, and published national and EU statistics, including birth rates and stillbirth rates. Rare disease databases were also searched.

Results The proportion of affected pregnancies was estimated as 3.17% (95% CI 2.93% to 3.43%), using a weighted average of the results from two cohort studies. Using birth rates from 2012 and adjusting for a pregnancy loss rate of 1/100 gave an estimated annual incidence of 3.33 per 10,000 EU population (95% CI 3.07 to 3.60 per 10,000 EU population). This fell below the EMA threshold of 5 per 10,000 EU population.

Conclusions Maternal vascular endothelial growth factor gene therapy for placental insufficiency was granted EMA orphan status in 2015 after we demonstrated that it is a rare, life-threatening or chronically debilitating and currently untreatable disease. Developers of other potential obstetric therapies should consider applying for orphan designation, which provides financial and regulatory benefits.

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Keywords

Orphan disease, placental insufficiency, fetal growth restriction, pregnancy, European Medicines Agency, incidence, prevalence

Tweetable Abstract

Placental insufficiency meets the European Medicines Agency requirements for orphan disease designation.

1. Introduction

For many years, the development of new obstetric therapies has been hampered by underinvestment from the pharmaceutical industry.[1-5] One way to address this is to consider whether new therapies qualify for orphan drug designation.[6] Orphan drug legislation was originally introduced in the United States in 1983 to encourage the development of medicines for rare diseases that might otherwise be financially unviable. Since then the European Union (EU), Australia, Singapore, Japan, Taiwan and South Korea have introduced their own legislation.[7-9]

The criteria for what constitutes a rare disease and the benefits that orphan drug designation bring vary between regulatory authorities. To qualify for European Medicines Agency (EMA) orphan designation a medicine must meet three key conditions (Table 1).[9, 10] The application for orphan status is made by the sponsor, either a commercial company or an academic institution (Figure S1).[11] If orphan status is granted the sponsor has access to EMA scientific advice at a reduced cost and receives 10 years of protection from market competition if the medicine is approved for use (Table S1).[12] Orphan drug designation can also be granted for repurposing licenced drugs. Successful applications bring the same benefits, but a separate application for marketing authorisation must be made for the rare disease indication using a different proprietary name.[13]

Despite the potential benefits, obstetric therapies are drastically under-represented among orphan drug designations. As of February 2018, the EMA had granted 1952 orphan drug designations and the US Federal Drug Agency (FDA) 4473. Of these, only 15 drugs are for the prevention or treatment of problems arising during pregnancy and only one, hydroxyprogesterone caproate, has been approved for use (Table 2).

The EVERREST consortium is an industrial academic health science partnership funded by the European Commission which aims to develop a new treatment for placental insufficiency manifesting as fetal growth restriction (FGR).[14] This treatment proposes to use maternal uterine artery application of an adenovirus gene therapy containing Vascular Endothelial Growth Factor (VEGF) to increase uteroplacental perfusion via reduced uterine artery contractility and to increase local angiogenesis.[15] In January 2015 one of the industrial partners, backed by the rest of the EVERREST consortium, successfully applied for EMA orphan drug designation for the use of maternal VEGF gene therapy to treat placental insufficiency.

In this article we outline how we estimated the annual incidence of placental insufficiency per 10,000 EU population. We believe that these methods could be applied to other obstetric diseases to form part of future successful orphan drug designation applications.

2. Methods

2.1. Defining the rare disease for orphan drug designation

Within the original title of the EVERREST Project, maternal VEGF gene therapy is described as a potential treatment for “severe early-onset fetal growth restriction”. However, EMA guidance states that the rare disease which the medicinal product will treat, prevent or diagnose should be “a distinct medical entity with specific pathological, histopathological or clinical characteristics”.[16]

The terms FGR and intrauterine growth restriction (IUGR) have been used inconsistently and

interchangeably over the years, most often to describe a fetus with an estimated fetal weight (EFW) <10th centile[17] or a fetus that has failed to achieve its growth potential.[18, 19] Small-for-Gestational Age (a definition based on a size or weight below a given threshold of the distribution, typically the 10th centile) has also been used as a proxy of FGR, adding more confusion. FGR is not a distinct disease but is instead a syndrome that can result from maternal, fetal and placental factors, alone or in combination. This made FGR unsuitable for our rare disease, since a therapy which increases uterine artery volume flow would not be expected to improve FGR resulting from causes such as aneuploidy.

In research and clinical practice, the shift from syndrome to disease is often made by defining a subset of FGR, for example FGR presenting before 32 weeks of gestation in the absence of fetal structural or chromosomal anomalies. However, for the purposes of orphan drug designation the EMA will generally not accept a subset of patients as a rare disease. Therefore, we needed to determine a suitable disease term with appropriate diagnostic criteria for our orphan drug application.

We searched national and international guidelines and consensus statements for definitions of FGR, and for alternative diagnostic terms and definitions. A PubMed search was performed for consensus development conferences, guidelines, and practice guidelines (search terms, automatically including alternate spellings, field terms and MeSH terms: “fetal growth restriction” “fetal growth retardation” “intrauterine growth restriction” “intrauterine growth retardation” “placenta”, limits: article type “Consensus Development Conference” OR “Guideline” OR “Practice Guideline”). The National Guideline Clearing House and International Guideline Library were searched for all guidelines relating to fetal growth restriction. Full lists of the current guidelines of the Royal College of Obstetricians and Gynaecologists (RCOG), the American Congress of Obstetrics and Gynecology (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC) were reviewed. We hand-searched the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) for relevant terms and potential definitions. As a reflection of current international opinion on diagnostic criteria we searched ClinicalTrials.gov and the ISRCTN Registry

using the term “growth restriction” and reviewed the inclusion criteria for any relevant multicentre trials. Final decisions were made through expert consensus within the EVERREST Consortium via face-to-face meetings and e-mail correspondence.

2.2. Estimating the annual incidence of placental insufficiency

For EMA orphan designation a condition should have a prevalence of not more than five per 10,000 of the EU population. For conditions lasting less than a year, for example those occurring only during pregnancy, the annual incidence must be less than five per 10,000 of the EU population. In estimating the annual incidence of obstetric conditions it is necessary to consider the proportion of pregnancies that are affected, the proportion of pregnancies which do not end in live birth, and national and EU birth rates.

2.2.1. Estimating the proportion of pregnancies affected by placental insufficiency

A literature search was conducted for epidemiological analyses of conditions and terms associated with placental insufficiency. Medline was searched using the terms “umbilical Doppler” AND “FGR” OR “fetal growth restriction” OR “fetal growth retardation” OR “IUGR” OR “intrauterine growth restriction” OR “intrauterine growth retardation” OR “small for gestational age”. Pubmed was searched using the terms “prevalence uteroplacental insufficiency”, “prevalence placental insufficiency”, “frequency uteroplacental insufficiency”, “frequency placental insufficiency”, “birth cohort ‘ultrasound’”, and “birth cohort Doppler”. No restriction was made on the language of the publication.

Studies were not included if they looked at first and second trimester prediction, or if they included only pregnancies with abnormal umbilical Doppler examination, for example to investigate outcomes. Studies were excluded if they did not use the 10th centile for EFW and/or birth weight,

considered only low EFW and/or birth weight **or** abnormal umbilical artery Doppler examination rather than a combination of the two, did not provide sufficient data to allow calculation of the proportion of affected pregnancies, or did not sample from a general obstetric population. Studies were included if part of the inclusion criteria for the study was the presence of a small-for-gestational age (SGA) fetus, as long as this was not also limited to pregnancies considered high- or low-risk.

The references of relevant studies, review articles, and national guidelines were searched by hand, including the Cochrane reviews of umbilical artery Doppler use in high-risk[20] and normal pregnancy[21], and theRCOG "Green-top Guideline No.31 The Investigation and Management of the Small-for-Gestational-Age Fetus".[18] Databases from the National Organization for Rare Disorders (NORD)[22], Orphanet[23], the Genetic and Rare Disease Information Centre (GARD)[24], and the Swedish Information Centre for Rare Diseases[25] were searched. The search terms were 'placenta', 'placental', 'insufficiency' and 'pregnancy'.

2.2.2. Calculating annual incidence in relation to the population of the European Union

The annual incidence was estimated by considering the proportion of pregnancies which the literature suggested would be affected (p), the number of potentially affected pregnancies over one year (n), and the size of the European Community population (pop), where:

$$\text{Annual incidence} = (p \times n)/pop$$

National and European statistics for birth rate give the number of live births per year (b) per 1000 population:

$$\text{Birth rate} = (1000 \times b)/pop$$

However, the number of potentially affected pregnancies (n) needs to include not only live births but also pregnancies which could have been affected but ended in termination, miscarriage or stillbirth.

If we add in an inflation factor (i) to account for these pregnancies then:

Annual incidence per 10,000 = p x 10 x birth rate x i

2.2.3. Estimating the proportion of potentially affected pregnancies which do not end in live birth

Since placental insufficiency cannot be diagnosed in the first trimester we did not need to adjust for pregnancies ending in miscarriage or termination in the first trimester. In order to correct for later pregnancy loss we reviewed national and European statistics on termination of pregnancy, miscarriage and stillbirth. Further data on elective termination of pregnancy in severe early-onset placental insufficiency was acquired through local retrospective audit and further data on pregnancy loss rates was obtained by searching Medline using the terms "Fetal death"[MeSH or All fields] OR "Abortion, Spontaneous"[MeSH] OR "Stillbirth"[MeSH or All fields] OR "fetal loss" AND "Incidence"[MeSH] OR "Cohort Studies"[MeSH] OR "etiology" AND "Pregnancy Trimester, Second"[MeSH] OR "second trimester".

2.3. Patient involvement and core outcome sets

There was no public or patient involvement in this work nor were core outcome sets used.

2.4. Funding

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 305823. This research has been supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre (RS, ALD, DMP). The funders played no role in conducting the research or writing the manuscript.

3. Results

3.1. Defining the disease for an orphan designation

We decided that the term 'placental insufficiency' best reflected the distinct medical condition which maternal VEGF gene therapy aimed to treat. We defined the diagnostic criteria as an estimated fetal weight (EFW) below the 10th centile in the presence of abnormal umbilical artery Doppler examination, including a pulsatility index (PI) above the 95th centile, absent end-diastolic flow (EDF) and reversed end-diastolic flow.

Placental insufficiency is recognised within the ICD 10 classification 036.5: "maternal care for poor fetal growth due to placental insufficiency". It is also recognised and described by national guidelines; in the context of a fetus with an EFW below the 10th centile the ACOG states that "increased impedance in the umbilical artery suggests that the pregnancy is complicated by underlying placental insufficiency"[17], while the SOGC states that "Doppler studies of the uterine and umbilical arteries, together with ultrasound assessment of placental morphology, may be used to establish a diagnosis of placental insufficiency".[19] An EFW or AC <10th centile with absent or reversed EDF formed part of the eligibility criteria for the UK trial of Sildenafil therapy in dismal prognosis early-onset intrauterine growth restriction (STRIDER, ISRCTN39133303) while an AC <10th and umbilical artery PI >95th centile constituted IUGR in the Trial of Umbilical and Foetal Flow in Europe (TRUFFLE, ISRCTN56204499).

Since our successful orphan drug application an International consensus definition of FGR has been published, which includes within its definition of early FGR an EFW <10th centile with an umbilical artery PI >95th centile.[26]

3.2. Annual incidence of placental insufficiency

3.2.1. The proportion of pregnancies affected by placental insufficiency

Three published studies were identified from which it was possible to estimate the proportion of pregnancies affected by placental insufficiency (Table 3).[27-29] A further 11 studies were assessed for eligibility but not included in the incidence estimate, either because they did not use a general obstetric population[30-34], because they used measures of size other than an EFW <10th centile[30, 33, 35-39] or because they used alternative measurements or thresholds to assess the umbilical artery Doppler velocimetry[30, 31, 33, 36-38, 40] (Table S2, Figure S2[41]). The only database to return a relevant finding under any of the search terms was GARD, which includes the category 'placenta disorders'. Within this category no further definition was given and no information on prevalence or incidence was included.

The proportion of affected pregnancies was estimated using a weighted average of the results from the studies by Unterscheider et al.[27] and Figueras et al.[28]. The results of the third study by Davies et al. were considered less reliable because the ultrasound technology available at that time may have led to an underestimation of affected pregnancies; these results were therefore excluded.[29] Using the Wald method to calculate the 95% confidence intervals gave an estimate for the proportion of affected pregnancies of 3.17% (95% CI 2.93% to 3.43%).

3.2.2. Accounting for pregnancies which do not end in live birth

Although national statistics were available for the number of pregnancies ending in elective termination each year, the majority of these terminations were before 20 weeks of gestation, at a point when placental insufficiency would not be diagnosed. For example, in England and Wales in 2013 only 2753 terminations were carried out at or after 20 weeks of gestation, less than 0.004% of the 698,512 live births for that year.[42] It was agreed, therefore, that pregnancies ending in elective termination should not be considered as part of the total number of potentially affected pregnancies.

National statistics were also available for the rates of stillbirth or late fetal death per 1000 live births, equating to between 0.33 and 0.49% of pregnancies. However, there was considerable national variation in how these terms were defined (Table S3). No national statistics were available for pregnancies ending earlier in gestation or with a smaller fetal size than that defined as stillbirth or late fetal death.

In turning to the literature, the best quality data came from a cohort of 264,653 women screened for Down's syndrome in Ontario, Canada between October 1995 and September 2000.[43] 1632 of these pregnancies (0.62%) ended in spontaneous fetal loss after 15 weeks of gestation. However, since older and smaller studies had reported up to 1.1% of pregnancies ending in fetal loss in the second or third trimesters[44, 45], we decided to take a conservative estimate of 1%, giving an inflation factor of 100/99.

3.2.3. Annual incidence in relation to the population of the European Union

Using the estimated proportion of affected pregnancies, national and EU birth rates from 2012 and an inflation factor of 100/99, we estimated the annual incidence of placental insufficiency per 10,000 population (with 95% confidence intervals) for the 28 countries in the EU at the time of our application in 2015 and for the European Union as a whole (Figure 1). The estimated annual incidence was 3.33 per 10,000 EU population (95% CI 3.07 to 3.60 per 10,000 EU population), which fell below the EMA threshold of five per 10,000 EU population.

Differences in national birth rates, however, led to considerable variation in annual incidence between countries. At the request of the EMA we performed additional sensitivity analyses to explore the potential effect of a changing birth rate or a rise in the proportion of pregnancies affected by placental insufficiency. These showed that the estimated annual incidence of placental insufficiency only rose above five per 10,000 EU population with a 55% or more rise in the EU birth rate or with 4.8% or more of pregnancies being affected.

4. Discussion

4.1. Main Findings

We have demonstrated that placental insufficiency meets the EMA criteria for a rare disease, with an estimated annual incidence of 3.33 per 10,000 EU population. This highlights that obstetric diseases do not necessarily have to be 'rare' in pregnancy (i.e. <5/10,000 pregnancies) in order to qualify as being rare on a population basis.

4.2. Additional requirements for EMA orphan drug designation

In order to be granted EMA orphan drug designation not only must the disease targeted be rare but it must also be life-threatening or chronically debilitating. Furthermore, the sponsor must justify the medical plausibility of the drug in question.

In the case of placental insufficiency, the risks of fetal or neonatal death or long-term disability for the fetus were easy to demonstrate. Histological studies have found that placental insufficiency contributes to between 22% and 49% of stillbirths.[46-48] Babies who survive a pregnancy complicated by placental insufficiency have long-term effects resulting from small size, often combined with iatrogenic preterm delivery, which creates a high risk of neonatal morbidity and mortality. The TRUFFLE study looked at the outcomes for 503 fetuses diagnosed with placental insufficiency between 26 and 32 weeks gestation.[49] Twelve fetuses (2.4%) died *in utero*, and a further 27 infants (5.4%) died during their time on the neonatal intensive care unit. Overall 24% of surviving infants experienced severe morbidity, including bronchopulmonary dysplasia, Grade III or IV germinal matrix haemorrhage, Grade II or III cystic periventricular leukomalacia, necrotising enterocolitis, or proven sepsis. At 2-year follow-up 10% of the children assessed (39/402) showed evidence of neurodevelopmental impairment.[50]

Of particular importance to the EMA was the potential impact of placental insufficiency on the

pregnant woman. This included the potential for Caesarean section, including classical Caesarean section, and the resulting increase in maternal morbidity and mortality.[18, 46, 51, 52] The EMA also considered the psychological impact on the mother of stillbirth or neonatal death[53] and the potential for co-existing pre-eclampsia.

The medical plausibility for maternal VEGF gene therapy is based on the observation that reduced uterine blood flow is a key pathology in placental insufficiency[54, 55], and that manipulation of VEGF expression can improve uterine blood flow, increase uterine artery relaxation and endothelial nitric oxide synthase (eNOS) production, and increase local angiogenesis.[56, 57] In preclinical animal models we have previously shown that local maternal VEGF gene transfer to the utero-placental circulation using adenovirus vectors increases uterine blood flow, attenuates constriction of the uterine arteries and increases angiogenesis[58]; these changes result in improved growth of severely growth restricted fetuses.[59-62]

4.3. Strengths and Limitations

Our work provides an insight into a route which so far few obstetric researchers have taken. Maternal VEGF gene therapy is one of only five obstetric therapies to receive EMA orphan drug designation. We hope that explaining the process and benefits of applying for orphan drug designation will encourage other academic and industry researchers to consider it.

It is important to note that our study only provides an estimate for the number of affected pregnancies in the EU. Our calculations involve a number of assumptions and our estimate for the proportion of affected pregnancies is based on the weighted average of only two studies. The relative scarcity of applicable studies in part reflects the heterogeneity in the criteria used in the literature to identify FGR and assess placental function.

For researchers in the United Kingdom (UK) there is also uncertainty about how EMA orphan drug designation will apply after the UK's exit from the EU. According to Article 2 of Regulation (EC) No 141/2000 the sponsor of an orphan medicinal product designation, whether a commercial company or an academic institution, must be established in the European Economic Area (EEA). In June 2018, all UK holders of orphan drug designation were advised to transfer designation to a holder established in the EEA.[63]

Orphan drug legislation alone will not overcome all the challenges involved in developing new obstetric therapies. In order to consider orphan drug designation, there must be a drug to test and licence. This stage on the translational pathway can only be reached once the pathophysiology of the condition has been elucidated and a potential therapeutic target identified. In recent years attention has turned to careful phenotyping of the three great obstetric syndromes, FGR, pre-eclampsia and preterm labour, to help pick apart the different underlying causes.[64, 65] More work is still needed in this area however, especially since the current heterogeneity within these three 'diseases' also complicates the design and conduct of clinical trials for obstetric therapies. This, in turn, increases the risk that a pharmaceutical company will not see a return on their investment and so deters their participation in the field.[4, 66]

4.4. Interpretation

In obstetrics, the first orphan drug designations were for prevention of preterm birth in 1994 and for treatment of severe hypertension associated with pre-eclampsia in 2004 (Table 2). Subsequently there have been a further ten successful applications, but none for placental insufficiency or FGR. The reason for this may be the apparent heterogeneity of the condition and the lack of knowledge about the correct calculation of the incidence of placental insufficiency as a rare disease.

5. Conclusion

Current levels of investment in obstetric therapies are not proportionate to the degree of unmet clinical need. Orphan drug designation could offset some of the costs of developing obstetric therapies, rendering them more financially attractive for investors. By sharing knowledge and experience, and through international multidisciplinary collaboration such as is seen in the EVERREST EU FP7 consortium, clinical academics, researchers, investors and industry will play a vital role in advancing the field of obstetric research. We hope that our successful application for orphan drug designation can provide an example to support future applications for maternal and fetal therapies.

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Disclosure of Interests: JM, ALD and DMP are shareholders of Magnus Growth, a company that is aiming to take to market a new treatment for placental insufficiency. JM is also an inventor of the patent for “the use of VEGF in the treatment of foetal growth retardation” and an unremunerated director of Magnus Growth. PB has received grants and personal fees from the MRC, and grants from NIHR and the Wellcome Trust, unrelated to the submitted work. PB was also Chair of the NIHR Health Technology Assessment Women's and Children's panel until November 2018.The remaining authors have no interests to disclose. Completed disclosure of interest forms are available to view online as supporting information.

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Table/Figure Caption List

Figure 1. Estimated annual incidence of placental insufficiency per 10,000 population, with 95% confidence intervals, for the 28 European Union countries (EU 28), based on 2012 birth rates.

Table 1. The three main requirements for a medicine to be eligible for European Medicines Agency orphan designation[9, 10]

Table 2. Products receiving orphan drug designation in USA or Europe for the prevention or treatment of obstetric conditions

Table 3. Summary of the included literature on the proportion of pregnancies affected by placental insufficiency

Figure S1. Flow chart for the application process for EMA orphan drug designation as of October 2018.[11] This process may be subject to change and potential applicants are advised to check the EMA website for up-to-date information.

Figure S2. Flow chart of literature reviewed in estimating the proportion of pregnancies affected by placental insufficiency. Adapted from the PRISMA flow of information diagram.[41]

Table S1. Benefits of EMA orphan drug designation [12]

Table S2. Summary of studies excluded from the analysis

Table S3. Examples of national stillbirth rates / late fetal death rates and definitions used by national statistics offices

Table 1. The three main requirements for a medicine to be eligible for European Medicines Agency orphan designation [9, 10]

1) The medicine is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating
2) The prevalence of the condition in the European Union is not more than 5 in 10,000 or it is unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development
3) No satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition

Table 2. Products receiving orphan drug designation in USA or Europe for the prevention or treatment of obstetric conditions

Product	Designation date	Designating authority	Indication	Current status
Progesterone	22 Dec 1994	FDA	Establishment and maintenance of pregnancy in women undergoing in vitro fertilization or embryo transfer procedures	Designated
Hydralazine	09 Apr 2004	FDA	Treatment of severe intrapartum hypertension (diastolic blood pressure greater than or equal to 110 or systolic blood pressure greater than or equal to 160) associated with severe preeclampsia/eclampsia of pregnancy	Designated
Misoprostol	10 Jan 2005	FDA	Treatment of intrauterine fetal death not accompanied by complete expulsion of the products of conception in the second and third trimesters of pregnancy.	Designated
Human cytomegalovirus immunoglobulin	30 Oct 2006	EMA	Prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection	Designated
Hydroxyprogesterone caproate	25 Jan 2007	FDA	Prevention of preterm birth in singleton pregnancies	Approved
S-nitrosoglutathione	13 May 2011	EMA	Treatment of pre-eclampsia	Designated
	28 Dec 2012	FDA	Treatment of severe pre-eclampsia	Designated
Human platelet antigen-1a immunoglobulin (anti-HPA-1a)	27 Oct 2011	EMA	Prevention of fetal and neonatal alloimmune thrombocytopenia	Designated
	27 Jun 2013	FDA		Designated
MCMV5322A/ MCMV3068A	22 Nov 2011	FDA	Prevention of maternal-fetal transmission of congenital CMV in pregnant women who acquire CMV infection during pregnancy	Withdrawn
Digoxin immune FAb	03 Feb 2012	FDA	Treatment of severe preeclampsia and eclampsia	Designated
Recombinant human alpha-1-microglobulin	04 Jul 2014	EMA	Treatment of pre eclampsia	Designated
Maternal vascular endothelial growth factor gene therapy	15 Jan 2015	EMA	Treatment of placental insufficiency	Designated
17-a-hydroxyprogesterone caproate (oral formulation)	01 Jun 2015	FDA	Prevention of preterm birth in women with a singleton pregnancy	Designated
Allogeneic ex-vivo expanded placental adherent stromal cells	29 Dec 2015	FDA	Treatment of severe preeclampsia	Designated
Recombinant human placental growth factor	16 Mar 2017	FDA	Treatment of severe preeclampsia	Designated
Human IgG1 anti-human cytomegalovirus monoclonal antibodies LJP538 and LJP539	18 Oct 2017	FDA	Prevention of congenital cytomegalovirus (CMV) infection following primary CMV infection in pregnant women	Designated

FDA: Federal Drug Agency, USA; EMA: European Medicines Agency.

Table 3. Summary of the included literature on the proportion of pregnancies affected by placental insufficiency

Author	Year of data collection	Country	Study design	Initial study sample	Participants excluded from analysis	Study sample analysed	Outcome	Estimated proportion of pregnancies affected
Unterscheider [27]	2010-2012	Ireland	Multicentre prospective observational study of hospitals covering >75% of all pregnant Irish women	1200 women with singleton pregnancies between 24 weeks and 36 weeks and 6 days gestation with an EFW < 10th centile	32 (2.7%) were excluded for chromosomal and/or structural abnormalities, 13 (1%) withdrew, 13 (1%) delivered outside of Ireland, and 26 (2.2%) were lost to follow-up	1116 pregnancies	37% (413/1116) of pregnancies with an EFW <10th centile had UmAPI >95th centile	3.7% (assuming 10% of pregnancies have an EFW <10th centile)
Figueras [28]	2002-2004	Spain	Single centre retrospective cohort study	8935 women with singleton pregnancies.	296 (3.3%) were excluded because of multiple pregnancies, 180 (2%) because of congenital anomalies, and 932 (10.4%) because of incomplete maternal or neonatal data	7645 pregnancies	19% (70/369) of pregnancies identified as having an EFW <10th centile antenatally had UmAPI >95th centile. Another 594 babies had a birth weight <10th centile.	2.4% (assuming the same proportion of UmAPI >95th centile in identified and non-identified SGA babies)
Davies [29]	1989	United Kingdom	Single centre randomised controlled trial of Doppler ultrasound monitoring vs. routine care	2600 women with singleton pregnancies	106 (4.1%) were excluded because they delivered elsewhere, 8 (0.3%) because they did not have a live fetus at the time of enrolment, 2 (0.07%) because of multiple pregnancies, and 9 (0.3%) because of missing data	1246 pregnancies monitored by Doppler ultrasound	One pregnancy with UmAPI >95th centile and birthweight <10th centile	0.08%

EFW=estimated fetal weight, UmAPI=umbilical artery pulsatility index