LANDSCAPE OF MEDICINES DEVELOPMENT FOR FIVE PREGNANCY-RELATED CONDITIONS 2000–2021

AIM
ACCELERATING
INNOVATION FOR MOTHERS

CONTENTS

1 INTRODUCTION

Despite improvements in maternal health outcomes over the last two decades, approximately 295,000 women still died from pregnancy-related causes in 2017, the vast majority in low- and middle-income countries (LMICs).[1] The prioritisation of maternal health within the Sustainable Development Goals (SDGs) – and the Millennium Development Goals before them – has focused largely on improving access to and quality of existing interventions and services. While this has had positive outcomes – including a 38% drop in the global maternal mortality ratio between 2000 and 2017[2] – there has been little attention or credence given to biomedical research and development (R&D) for new or improved maternal health medicines. This is a gap. Current medicines available to prevent or treat pregnancy-related conditions responsible for the majority of maternal and neonatal deaths – including postpartum haemorrhage, preeclampsia/eclampsia and preterm labour/birth – are either suboptimal, not appropriate for LMIC contexts, or both. For others, such as intrauterine growth restriction and intrapartum foetal distress, no effective medical management exists at all.

There are several reasons for this. Primarily, industry's profit-driven R&D model is discouraged by a perceived low return on investment (a small market of pregnant women, with short-lived pathologies, many of whom are in LMICs with limited ability to pay), and the heightened litigiousness of developing drugs for use in pregnant women, particularly following the fall-out from thalidomide. Indeed, including women at all – let alone pregnant women – in drug R&D is a well-documented problem.[3] Without disruption, this current model will ensure little progress is made to meet the SDGs, and avoid countless more deaths, particularly for women in LMICs.

The 'Accelerating Innovation for Mothers' (AIM) project – spearheaded by the Concept Foundation and delivered in partnership with Policy Cures Research and Burnet Institute – was created with the aim of fostering greater investment in and development of critical maternal health medicines for five significant pregnancy-related conditions, where biomedical product gaps exist:

- preterm labour/birth (PTL/PTB)
- preeclampsia/eclampsia (PE/E)
- intrauterine growth restriction (IUGR)
- postpartum haemorrhage (PPH)
- intrapartum foetal distress (herein 'foetal distress')

1 World Health Organization, 'Trends in Maternal Mortality 2000 to 2017: Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division: Executive Summary', 2019, https://apps.who.int/iris/handle/10665/327596.

2 World Health Organization. 2019

3 Committee on Ethics, 'ACOG Committee Opinion No. 646: Ethical Considerations for Including Women as Research Participants', *Obstetrics and Gynecology* 126, no. 5 (November 2015): e100-107, https://doi.org/10.1097/AOG.0000000000001150.

The roadmap for this endeavour has included, in its earliest phases, a rich body of foundational research aimed at uncovering the epidemiological impact, market drivers and barriers, funding and governance options, as well as the current and historical landscape of product research and development (R&D) for these five conditions.

To date, a landmark paper from 2008, *Market Failure and the Poverty of New Drugs in Maternal Health* by Nicholas Fisk and Rifat Atun, has served as the gold standard review of maternal health medicines in clinical development. Fisk and Atun shed light on the paucity of drugs specifically for obstetric conditions, the miniscule number of newly licensed drugs in the two decades preceding their research, and the absence of new drug classes under investigation. They identified 67 drugs with maternal indications (the majority for PTL/PTB) and just 17 drugs under active development as of November 2007.[4] This lack of investment in – and urgent need for more – medicines development expressly for and involving pregnant women was echoed in a 2016 perspective by Lucy Chappell and Anna David *Improving the pipeline for development and testing pharmacological treatments in pregnancy*.[5]

In the intervening years, the field of maternal health medicines development has continued to be stunted by a range of clinical, ethical, financial and legal barriers. That said, general advancements in clinical research and medicines development during this period, as well as the growth of innovative push-pull mechanisms – including an upspring of novel product development partnerships for neglected diseases and conditions – and the creation of the AIM project partnership to accelerate progress in this field, has fuelled motivation to build on Fisk and Atun's important research and provide an updated landscape analysis of this targeted subsection of obstetric medicines R&D.

From the outset, we hypothesised that, for a variety of financial or operational reasons, many investigations for candidate medicines for these conditions could have easily fallen out of active clinical development or simply lost momentum, despite being potentially promising preventive or therapeutic solutions. As such, we felt it was important to broaden the scope of the research to look not only at medicines in active development, but also at those that had entered preclinical study or clinical development and stalled, stopped, or failed in recent times.

4
Nicholas M Fisk and Rifat Atun, 'Market Failure and the Poverty of New Drugs in Maternal Health', *PLoS Medicine* 5, no. 1 (January 2008), https://doi.org/10.1371/journal.pmed.0050022.

5
Lucy C. Chappell and Anna L. David, 'Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy', *PLOS Medicine* 13, no. 11 (1 November 2016): e1002161, https://doi.org/10.1371/journal.pmed.1002161.

In addition, a blooming field of basic research into the underlying aetiology of these conditions – particularly for PE/E and PTL/PTB – has in recent years unveiled previously elusive mechanisms of pathogenesis, in turn providing a plethora of research avenues with potential therapeutic applications. For this reason, we expanded our scope to also capture candidates in preclinical and discovery stages. Accordingly, we sought to develop a comprehensive database of medicines that have been investigated at any point and at any stage of development in the past 20 years (2000–2021), for these five pregnancy-specific conditions.

II METHODOLOGY

Our approach was to create a comprehensive database profiling all medicines (drugs, biologics and dietary supplements) investigated since 2000 for each pregnancy-related condition. Medicines could be applicable for use in any context, including high-income country (HIC) and low- and middle-income country (LMIC) contexts, or be targeted towards special subgroups, such as PPH prevention for women with Von Willebrand's disease. For inclusion in the dataset, the medicine candidates needed to:

- be small molecules (drugs), biologics or dietary supplements, with no restrictions: candidates could be entirely new entities; existing/repurposed/label extensions; new formulations or dosing of existing/registered medicines
- have an indication or multiple indications related to the project's five identified pregnancy-related conditions: preterm labour/birth, preeclampsia/ eclampsia, intrauterine growth restriction, postpartum haemorrhage, foetal distress
- either be in active development, or have been at one point between 2000 and 2020 (public announcements and updates on relevant candidates made between January and May 2021 were also captured in their respective profiles)
- be either investigated for clinical use and/or used currently in clinical treatment of the five identified conditions

Specific exclusions were:

- devices, diagnostics, and other non-medicine-related biomedical products with indications specific to the project's five pregnancy-related conditions

We undertook a series of partially sequential, partly overlapping, but mutually reinforcing steps to develop a database of candidate profiles. These were:

1. identify and validate candidates through multiple sources that are or were in the pipeline for each of the identified pregnancy-related conditions since 2000
2. collect information on the candidate's preclinical or clinical development, and associated data
3. research additional context around the product (e.g. development history, stakeholders)
4. validate and sense check candidate profiles through independent, external reviews by clinical research specialists in the field

DATA REQUIREMENTS

These four research steps were borne out of an initial data requirement gathering exercise, whereby we agreed to and defined data fields to be captured for each candidate (where available and verifiable) (see Table 1).

Table 1

Data fields captured for each candidate (where available)

Candidate profile	Linked clinical trial (CT) data
• Candidate ID (internally assigned number) • Candidate name • Alternative/previous candidate names • Pregnancy-specific condition (primary) • Indication • Archetype • Product type • WHO ATC code • Medical subject headings • Pharmacological subgroup • Route of administration • Target • Mode of action • Clinical use status • Current R&D stage (for this pregnancy condition) • Highest R&D stage (for any condition) • Development status • Inactive development type (as appropriate) • Key features/challenges • Most recent update • FDA pregnancy labelling/pregnancy risk summary • Preclinical results status • Preclinical results type (as appropriate) • Preclinical results source (as appropriate) • Investigated for other indications (y/n) • Other indications (as appropriate) • Developer(s) • Patent • CAS number • Chemical name	• CT title • CT number • CT last updated • CT phase • CT source • CT status • CT terminated type (as appropriate) • CT terminated reason (as appropriate) • CT description • CT start date • CT start type (actual vs planned) • CT end date • CT end type (actual vs planned) • CT location(s) • CT enrolment • CT results status • CT results type (as appropriate) • CT results source (as appropriate) • CT sponsor(s) • CT collaborator(s)

For each field, we developed a definition, data input description and sample data type classification (for example, numeric, free-text, or defined list, etc.), as well as guidance notes where relevant, to ensure standardised data entry across researchers/enumerators (see Annexe 1).

METHODS AND SOURCES

STEP 1: INITIAL CANDIDATE IDENTIFICATION

Various sources were utilised to uncover and identify a total of 444 unique candidates.

A We searched Adis Insight[6] – a leading drug development database – to retrieve a comprehensive output of relevant pipeline drugs related to the project's five pregnancy-related conditions. The platform returns detailed information on drugs, candidate deals, clinical trials, safety, patents, and other historical information useful for building candidate profiles. Information is full via subscription (our approach) or limited via open source. We searched utilising Adis Insight's inbuilt 'by indication' function, which classifies drugs using a standardised list of indications. Accordingly, free-text searches by indication are not possible. We therefore used search terms that were the most relevant available indications in the database to the five conditions investigated. These were: "Preterm-labor" OR "Preterm labour" OR "Preterm birth" OR "Preterm-delivery"; "Pre-eclampsia" OR "Eclampsia"; "Foetal-growth-retardation" OR "Fetal growth retardation"; "Postpartum-bleeding" OR "Postpartum haemorrhage" OR "Postpartum-hemorrhage" OR "Delayed-postpartum-haemorrhage"; "Foetal-distress" OR "Fetal distress".

"Drug" outputs were retrieved and unique candidates and associated data formatted, extrapolated, and transposed into our database. Of note, postpartum haemorrhage and foetal distress returned zero "drug" profiles but a number of associated "clinical trial" outputs (39 and one respectively). For these conditions, we instead reviewed these linked clinical trials to identify unique candidates for inclusion in the database. Adis Insight search results were retrieved in January 2021 (see Table 2).

6 https://adisinsight.springer.com/

Table 2

Number of candidates retrieved from Adis Insight by condition

	PTL/PTB	PE/E	IUGR	PPH	Foetal distress
Number of unique candidates identified via Adis Insight	30^	14^	3^	12*	1*

^ Candidates identified through 'drug' outputs
* Candidates identified through 'clinical trial' outputs

B We cross-checked candidates identified through Adis Insight with those from Citeline's Pharmaprojects[7] – a paid database output that offers end-to-end tracking of the global pharma R&D pipeline. The output was initially procured and retrieved by Concept Foundation in March 2020. Cross-check was performed in January 2021. All candidates identified in the Pharmaprojects search results were present in the Adis Insight results. Adis Insight returned additional relevant candidates not present in the Pharmaprojects output.

C We requested a data export from the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)[8] – the most comprehensive list of global clinical trials available. The following search terms were used to retrieve five datasets related to the project's pregnancy-specific conditions in January 2021: "preterm labour" OR "preterm birth"; "pre-eclampsia" OR "preeclampsia"; "Impaired fetal growth" OR "IUGR" OR "fetal growth restriction"; "postpartum haemorrhage" OR "obstetric haemorrhage"; "fetal distress". Clinical trials were scoped for relevance, which we defined as an investigation of one or more drugs, biologics, or dietary supplements with a primary and/or secondary outcome measure matching at least one of the five pregnancy-related conditions. This step served a dual function of uncovering additional candidates for inclusion that had not yet been identified (see Table 3), as well as capturing and linking clinical trial data to candidates marked for inclusion in the database (see Step 2 below for more information).

7 https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/pharmaprojects

8 https://apps.who.int/trialsearch/

Table 3

Number of candidates retrieved from ICTRP by condition

	PTL/PTB	PE/E	IUGR	PPH	Foetal distress
Number of unique clinical trials returned via ICTRP	3,691	907	298	460	93
Number of unique clinical trials identified as in scope	363	304	72	267	4
Number of unique candidates identified via in scope clinical trials	41	60	25	27	2
Number of additional candidates identified via ICTRP not already identified via Adis Insight	32	57	24	17	1

D We searched PubMed[9] for relevant literature to validate already identified and uncover new candidates for inclusion. We anticipated this would include several candidates in preclinical development, and considered search terms that would return information on novel or innovative R&D. We searched using the same pregnancy-specific condition search terms used in our ICTRP search (see above), combined with the following additional terms: "prevention"; "treatment"; "innovation"; "discovery"; and "preclinical". We included additional search terms to validate findings: drugs; medicine; and "biologics". For each pregnancy-specific condition, we therefore performed the following searches:

- "*condition search term*" + "prevention" + "innovation"
- "*condition search term*" + "treatment" + "innovation"
- "*condition search term*" + "prevention" + "discovery"
- "*condition search term*" + "treatment" + "discovery"
- "*condition search term*" + "prevention" + "preclinical"
- "*condition search term*" + "treatment" + "preclinical"
- "*condition search term*" + "prevention" + drugs + medicine
- "*condition search term*" + "treatment" + drugs + medicine
- "*condition search term*" + "prevention" + "biologics"
- "*condition search term*" + "treatment" + "biologics"

9 https://pubmed.ncbi.nlm.nih.gov/

PubMed searches were conducted between March and April 2021. Returned paper titles and abstracts were reviewed for relevance. Relevant publications were reviewed in full. Unique and in-scope candidates were added to the database, or additional data on existing candidates already entered in the database was captured (see Table 4).

Table 4

Number of publications (total/relevant*) retrieved, and candidates (additional) identified from PubMed by condition

	PTL/PTB	PE/E	IUGR	PPH	Foetal distress
"*condition*" + "prevention" + "innovation"	49/13	31/12	6/2	20/9	2/0
"*condition*" + "treatment" + "innovation"	32/6	25/9	8/2	21/3	3/0
"*condition* + "prevention" + "discovery"	34/11	0/0	3/0	1/1	0/0
"*condition*" + "treatment" + "discovery"	32/10	36/15	6/2	6/2	0/0
"*condition*" + "prevention" + "preclinical"	34/14	25/19	7/6	2/1	0/0
"*condition*" + "treatment" + "preclinical"	36/11	41/29	11/10	1/1	0/0
"*condition*" + "prevention" + drugs + medicine	104/60	84/44	14/7	51/42	2/2
"*condition*" + "treatment" + drugs + medicine	126/62	149/77	25/13	54/38	8/5
"*condition*" + "prevention" + "biologics"	2/1	3/2	0/0	0/0	0/0
"*condition*" + "treatment" + "biologics"	3/2	6/4	0/0	1/0	0/0
Number of additional candidates identified via PubMed not already identified via ICTRP and Adis Insight	116	80	35	10	9

* Relevant papers are those in which we identified additional or validated existing candidates for any of the five conditions

E We searched the grant databases of three of the largest global funders of medicines development to validate existing and find new candidates (particularly those in preclinical/discovery stage): the United States National Institutes of Health (US NIH)'s RePORTER[10]; the European Union/Commission's CORDIS[11]; and the Bill & Melinda Gates Foundation's grants database (data supplied from the foundation). For all databases, we searched using the same pregnancy-specific condition search terms used for ICTRP (see above). For RePORTER, we retrieved all grants dating from 2000 to present. For CORDIS, we retrieved four datasets relating to different EC programme cycles: FP5 1998–2002; FP6 2002–2006; FP7 2007–2013; and Horizon 2014–2020. For Gates Foundation, we searched datasets ranging from 2014–2019 inclusive (dates supplied and available for review). All datasets were retrieved and scoped for relevance between March and April 2021. Profiles were created for new candidates or information added to existing candidates, as appropriate (see Table 5).

10 https://reporter.nih.gov/

11 https://cordis.europa.eu/

Table 5

Number of grants and candidates retrieved from RePORTER, CORDIS and Gates Foundation databases by condition

	PTL/PTB	PE/E	IUGR	PPH	Foetal distress
RePORTER					
Number of grants returned via RePORTER	587	198	152	31	65
Number of grants identified as in-scope	8	14	1	1	0
Number of unique candidates identified via in-scope grants	9	13	1	1	0
Number of additional candidates identified via in-scope grants not already identified elsewhere	0	2	1	0	0
CORDIS					
Number of grants returned via CORDIS	54	23	31	39	4
Number of grants identified as in-scope	0	0	0	0	0
Number of unique candidates identified via in-scope grants	0	0	0	0	0
Number of additional candidates identified via in-scope grants not already identified elsewhere	0	0	0	0	0
Gates Foundation					
Number of grants returned via database	4	30	32	4	0
Number of grants identified as in-scope	2	0	0	3	0
Number of unique candidates identified via in-scope grants	1	0	0	1	0
Number of additional candidates identified via in-scope grants not already identified elsewhere	0	0	0	0	0

STEP 2: LINKING PRECLINICAL AND CLINICAL DEVELOPMENT DATA

For candidates in clinical development, we collected relevant clinical trial data through a few sources. Primary candidate identification through Adis Insight[12] (Step 1) also provided linked clinical trials. These were scoped for relevance, and manually uploaded to the clinical trial entries in our database. Next, we datamined the datasets retrieved from the WHO International Clinical Trials Registry Platform (ICTRP)[13] as described above. We scoped every clinical trial entry in the datasets for each pregnancy-specific condition. Relevant trials were marked for inclusion and assigned to a candidate (or multiple if more than one candidate was being investigated). Given the size (in the thousands), this data was then uploaded to the clinical trial entries in our database using a coded, automated upload. We cross checked ICTRP clinical trials with those from Adis Insight to rule out duplicates. We also cross-checked candidates against relevant national clinical trials registers[14], if additional clinical trial information was needed. Clinical trial data scope and upload was performed between February and March 2021.

For candidates in preclinical development, results were sourced through PubMed searches between March and April 2021 (see Step 3).

STEP 3: COMPLETING CANDIDATE PROFILES

Much of the candidate information needed to complete candidate profiles was provided through Steps 1 and 2. The clinical trials served as a key source of information for completing candidate profiles, including information on route of administration, target, mode of action, and development status (among others). However, to ensure all fields were completed, we utilised academic literature search engines/tools to source greater detail and context for the candidates identified in Steps 1 and 2. Primarily, we searched PubMed[15] using the candidate name/s, and reviewed relevant literature retrieved (including that already sourced in Step 1) to verify and cross reference information as needed. This type of information helped us to understand the development status/activity of candidates, as well as provided deeper information on those in preclinical development. Where possible, all references were standardised to PubMed URLs.

12 https://adisinsight.springer.com/

13 https://apps.who.int/trialsearch/

14 https://sites.google.com/a/york.ac.uk/yhectrialsregisters/home/clinicaltrials

15 https://pubmed.ncbi.nlm.nih.gov/

For candidates that failed or stagnated, additional information (on top of that provided by Adis Insight) was searched via relevant regulatory websites, such as the US Food and Drug Administration (FDA)[16] and European Medicines Agency (EMA)[17]. Information for other database fields was sourced from a number of reliable online sources, including DRUGBANK Online[18], PubChem[19], the US National Library of Medicine's Medical Subject Headings (MeSH) portal[20], and other websites as needed.

Additional candidate profile information was conducted between January and May 2021, concurrently with the steps outlined above.

STEP 4: EXTERNAL VALIDATION AND SENSE CHECKING

Following database completion, a series of internal and external, independent reviews were undertaken to clean and validate the data. Internally, each candidate was reviewed for content, consistency, and logic by a minimum of two and often three or four individuals. Data cross checking and cleaning was conducted in a rigorous, sequential manner. Some steps served to clean and standardise the data, while others were intended to identify content or subject matter error. Illustrative content checks included, for example, reviewing archetype against highest R&D stage (i.e., all 'repurposed' candidates needed logically to have a highest R&D stage as 'marketed'), or reviewing clinical use status by current R&D stage (i.e., all approved candidates needed logically to be Phase IV, with off label or not yet approved candidates preclinical through to Phase III).

An external review was also undertaken. We sought independent, specialist input from two external reviewers actively working on new drugs development for one or more of the pregnancy-related conditions under investigation (at the Ritchie Centre, Department of Obstetrics and Gynaecology, Monash University). The entire database was reviewed to validate candidates or identify known missing candidates; review the essential, standard labels for the candidates; review the fields related to clinical use case; and for each, recommend corrections, improvements, or additional details. Advisory input from the AIM team and the project's expert advisory committee was also sourced throughout data compilation, as needed.

16 https://www.fda.gov/home

17 https://www.ema.europa.eu/en

18 https://go.drugbank.com/

19 https://pubchem.ncbi.nlm.nih.gov/

20 https://meshb.nlm.nih.gov/search

KEY METHODOLOGICAL DECISIONS

As research unfolded and some new end-user requirements for the database were introduced, it was necessary to revisit, stress test, and occasionally make ongoing, minor adjustments or clarifications to the inclusion/exclusion criteria, as well as various database fields. Each change or refinement was made with the aim of maximising standardisation across the candidate profiles. These modifications were documented and include:

METHODOLOGICAL REFINEMENTS RELATED TO INCLUSIONS/EXCLUSIONS:

- Dietary supplements were broadly defined following the US FDA definition[21], but tailored for functionality and usability, for example to keep specific groupings of compounds together, such as polyphenols. Those specifically registered as a drug (such as N-acetyl cysteine) were kept as drugs. For inclusion, dietary supplements needed to be dosed formulations (i.e., food-based interventions such as 'beetroot juice' or 'chocolate' alone were not considered in scope).
- Candidates that addressed all stages of the pregnancy condition, including in some instances the postpartum period (e.g., postpartum preeclampsia) were included. However, candidates directed at postpartum conditions related to but not specifically targeted to the pregnancy-specific condition (e.g., cardiac disease in women who have had preeclampsia) were excluded.
- Antibiotics (e.g., azithromycin, erythromycin, clindamycin, amoxicillin, etc.) investigated in or used for preterm labour (to prevent ascending infection and inflammation during premature rupture of membranes (PROM) or as a prophylactic in women with intact membranes) were excluded. This was agreed to based on their broad applicability well beyond that of the pregnancy-specific condition in question; the large number of them (with potential to skew the dataset); and their very downstream position in treating each condition's pathology.
- Agents that inhibit uterine infection or inflammation (e.g., N-acetylcysteine, indomethacin, aspirin, progesterone, pravastatin, etc.) or maintain vaginal flora/pH were included. This was decided due to their specificity to the inflammatory pathways identified as precursors to a number of the pregnancy-related conditions, and their upstream position in treating each condition's pathology. Antenatal agents aimed at reducing consequences of preterm labour/birth (e.g., corticosteroids for foetal lung maturation) were included, given their frequent administration alongside tocolytics.

21 https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements

- Antihypertensives for preeclampsia/eclampsia (e.g., labetalol, methyldopa etc.) were included. Despite their broad applicability, they are critically used to prevent and treat preeclampsia/eclampsia, and as such are in scope.
- Broad haemostatic agents for treatment of general haemorrhage (e.g., prothrombin complex concentrate, fresh frozen plasma etc.) were included only if PPH was specifically indicated for its use, or was investigated as an outcome.
- Candidates used only for experimental purposes (e.g., as an experimental aid to elicit smooth muscle contraction or relaxation) were only included if reference was made to/the research was geared towards one or more of the pregnancy-specific conditions.

METHODOLOGICAL REFINEMENTS RELATED TO DATA FIELDS:

- *Archetype:* "Repurposed" candidates were any candidate previously or currently marketed for any other condition. "New chemical or biological entities (NCEs)" were candidates not already marketed for any condition (unless an NCE marketed for that pregnancy-related condition). We also considered candidates with new formulations or different routes of administration of existing medicines (e.g., inhalable oxytocin, heat stable carbetocin etc.) as NCEs (unless already marketed for something else).
- *Clinical use status:* If verified in the literature, drug databases, FDA/EMA sites, or by one or more clinical practitioners/experts that a candidate was approved and marketed for clinical use, or is advised for or frequently used off label for that condition in clinical practice, candidates were marked as such.
- *Current R&D stage:* Some candidates were in clinical development with no R&D stage specified in linked clinical trials, or stated as 'N/A' or 'unknown'. Others listed a variety of R&D stages amongst various clinical trials, including those marked as Phase IV even for candidates not yet marketed for that condition. To allocate a single, appropriate R&D stage to each candidate, we reviewed linked clinical trials against accepted definitions of each R&D stage (preclinical through to Phase IV), and assigned a phase based on trial descriptions.
- *Development status (active versus inactive):* Due to the often proprietary nature of R&D, information on the current development status of some candidates was not available in the public domain. To avoid labelling many candidates as development status 'unknown', it was agreed that active candidates would be any candidate with evidence of R&D within the last three years (since 2019). If no updates were made available on a candidate in the previous three years, or there was clear evidence of their discontinuation since then, they were marked as inactive.

- *Pharmacological subgroup:* This field was populated using either the WHO ATC 4th level classification for that drug or the FDC EPC classification.
- *Medical subject headings:* With numerous possible pharmacological and clinical classifications for medicines, as well as the great divergence in spelling protocols and naming conventions, the need for inclusion and standardisation of this information became paramount. It was decided that this field would be populated first through a search for the candidate in the NIH – Medical Subject Headings search engine[22]. Items listed under the field labelled "Pharm Action" were included. If the candidate was not listed, any other useful keywords that described the pharmacological or therapeutic uses for the candidate were included (e.g., Bronchodilator agents; Sympathomimetics; Tocolytic agents etc.).

MATERIALS AND PLATFORMS

Our database was built using Microsoft Lists and transposed to Microsoft Excel and Word. Our analyses were performed using Microsoft Excel.

LIMITATIONS

Our aim was to identify all medicines in development for these conditions since 2000, which we approached by utilising the comprehensive, multi-pronged search strategy described above. However, due to the proprietary nature of (and lack of publicly available information on) many, particularly preclinical, candidate investigations, we anticipate the data may have gaps with respect to the full body of research. We also acknowledge that the data sources used that rely on self-reporting by investigators (e.g., ICTRP) have their own inherent limitations, including potential for reporting biases arising from changes in adherence and utilisation over time. Lastly, readers should also note the data is up to date – and analyses drawn from the status of candidates – as of mid-2021.

22 https://meshb.nlm.nih.gov/search

III FINDINGS

First, we provide an overview of the overall volume, development status, archetype, product type, and R&D stage for all candidate medicines investigated across the five conditions. The conditions in question are certainly not homogenous in either clinical presentation, diagnosis, management, or general complexity, so while concatenating figures into a single picture is important for understanding the overall quantum of R&D in this space, the landscape varies dramatically across the conditions and these nuances should be factored into any overarching assessments. Subsequent condition-specific findings are also included in the below sections.

OVERVIEW

We identified a total of 444 candidates, of which 224 (50.4%) were in active preclinical/clinical development and 220 (49.6%) were inactive[23] (see Table 6). This does include some duplicate medicines that have been investigated for multiple conditions. In all, there were 344 truly unique candidates contained within the dataset. This consists of 276 medicines that were investigated for only one of the conditions and 68 investigated for two or more. (See Annexe 2 for a full list of candidates).

Table 6

Overall number and development status of candidates by condition

Condition	Development Status		Total
	Active	Inactive	
Foetal distress	1	10	11
Postpartum haemorrhage (PPH)	27	12	39
Intrauterine growth restriction (IUGR)	38	25	63
Preeclampsia/eclampsia (PE/E)	90	63	153
Preterm labour/birth (PTL/PTB)	68	110	178
Grand Total	**224**	**220**	**444**

23
If no updates have been made available on a candidate in the previous three years, they have been marked as inactive.

Two thirds of candidates for all conditions were repurposed (291 candidates, 66%), with the remaining (153 candidates, 34%) new chemical/biological entities (i.e., not marketed for any condition) (see Table 7). This divide becomes even more pronounced when we narrow our look at active candidates, 74% of which (166 candidates) were repurposed and 26% NCEs (58 candidates). Moreover, 81% of all new chemical/biological entity candidates (124) have only been investigated in preclinical stages, underscoring the dominance of repurposed medicines in the clinical development landscape for these conditions – where moving forward with promising candidates already marketed and proven safe in pregnancy is an attractive (and more pragmatic) option – and highlighting the structural challenges of advancing NCEs for obstetric conditions more broadly. Fear of teratogenicity is pervasive, so this is unsurprising: even marketed medicines and vaccines considered safe during pregnancy often base their recommendations on 'enough' pregnant women inadvertently being exposed, rather than on evidence from clinical trials.[24]

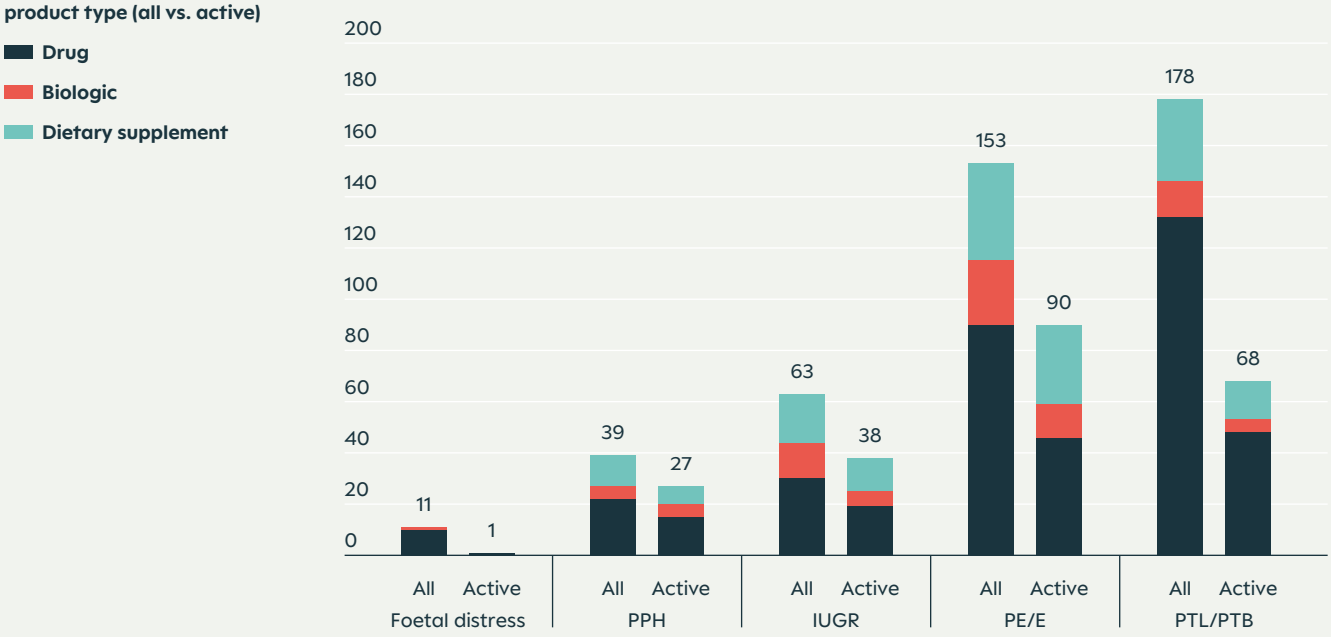
Table 7

Candidate archetype by condition

Condition	Archetype		Total
	New Chemical or Biological Entity	Repurposed	
Foetal distress	1	10	11
Postpartum haemorrhage (PPH)	13	26	39
Intrauterine growth restriction (IUGR)	19	44	63
Preeclampsia/eclampsia (PE/E)	38	115	153
Preterm labour/birth (PTL/PTB)	82	96	178
Grand Total	**153**	**291**	**444**

24
Elizabeth Wenqian Wang et al., 'SARS-CoV-2 Vaccination During Pregnancy: A Complex Decision', *Open Forum Infectious Diseases* 8, no. 5 (10 April 2021): ofab180, https://doi.org/10.1093/ofid/ofab180.

FIGURE 1
Number of candidates by condition and by product type (all vs. active)



In total, 64% (284) of the candidates were drugs, 13% (59) were biologics, and 23% (101 candidates) were dietary supplements.[25] The split of product type by condition is displayed in Figure 1. Although there are some interesting biologics under investigation across these conditions, their underrepresentation is perhaps not surprising, given their relatively high cost to research and manufacture.

Across drugs and biologics, an exciting body of research exists in the field of nanotechnology. This includes a number of nanoparticle-based candidates identified across all five conditions (eight for PTL/PTB, five for IUGR, two for PE/E, one for PPH, and one for foetal distress), which were included in the database. Some are duplicates of other candidates but with a novel, nanotechnology-based delivery approach (e.g., 'nifedipine' vs 'nifedipine in nanoparticle delivery' for PTL/PTB). However, we decided that nano-delivery was distinct enough to warrant separate candidate profiles and entries. Although many of these are labelled "inactive" due to a lack of recent updates, there is optimism around the future applicability of these technologies for the safe and directed treatment of serious pregnancy-related conditions.[26]

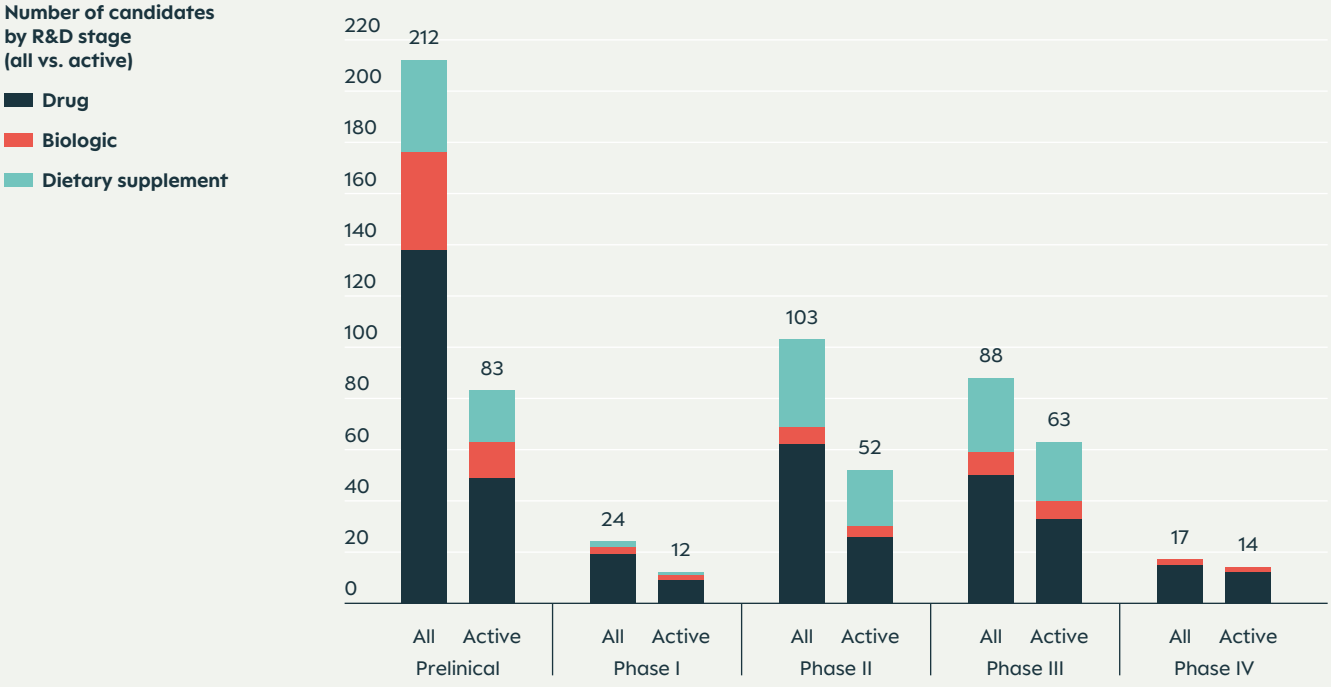
Across conditions, the landscape was skewed heavily by a large volume of preclinical candidates (212 candidates, 48%) (see Figure 2).[27] Notably, the majority of preclinical candidates were for PTL/PTB (107 candidates, 50% of all preclinical and 24% of all candidates).

25
More granular analyses of product distribution by R&D phase are included in the condition-specific sections below.

26
Natasha Pritchard et al., 'Nanoparticles in Pregnancy: The next Frontier in Reproductive Therapeutics', *Human Reproduction Update* 27, no. 2 (19 February 2021): 280–304, https://doi.org/10.1093/humupd/dmaa049.

27
To provide a clearer comparison of R&D stages, intermediate stages (e.g., Phase IIb, Phase I/II, Phase Ia) have been standardised to the most appropriate umbrella phase.

FIGURE 2
Number of candidates by R&D stage (all vs. active)



R&D stage breakdown by condition revealed a comparable landscape (in terms of proportion) for PTL/PTB, PE/E and IUGR (see Figure 3). For these, the largest volume of candidates was in preclinical development, a small proportion were in Phase I investigations, and there was a relatively even split of candidates in Phases II and III. This skew to discovery and preclinical candidates is probably reflective of a new, deeper understanding of these diseases' complex, multiple aetiologies – borne from insightful basic research – which now offers a number of potential therapeutic targets and research avenues. Dissimilarly, PPH had notably small proportions of preclinical and Phase I candidates and larger (and fairly equal) shares of candidates split across mid- and late stage clinical development (including the largest number and proportion of approved candidates in Phase IV post-marketing/surveillance studies). Although this shows promise, it's worth noting that – aside from heat stable carbetocin and oxytocin in uniject, technically both reformulations, and the latter of which is inactive – the advanced clinical pipeline for PPH reflects either Phase III trials of repurposed, and some already off label, medicines (e.g., misoprostol, tranexamic acid, Von Willebrand factor etc.), or Phase IV comparator and subpopulation studies on available uterotonics – as opposed to the advancement of a large number of new drugs for this condition. More detailed reflections on this are included in the PPH-specific section below. Foetal distress was an outlier, with very few candidates overall, and with all but one (a preclinical haemoglobin-vesicle via nanoparticle delivery, primarily investigated for PE/E and IUGR) in Phase II (ten candidates, 91%).

FIGURE 3
Number of candidates by R&D stage and by condition

- Preclinical
- Phase I
- Phase II
- Phase III
- Phase IV

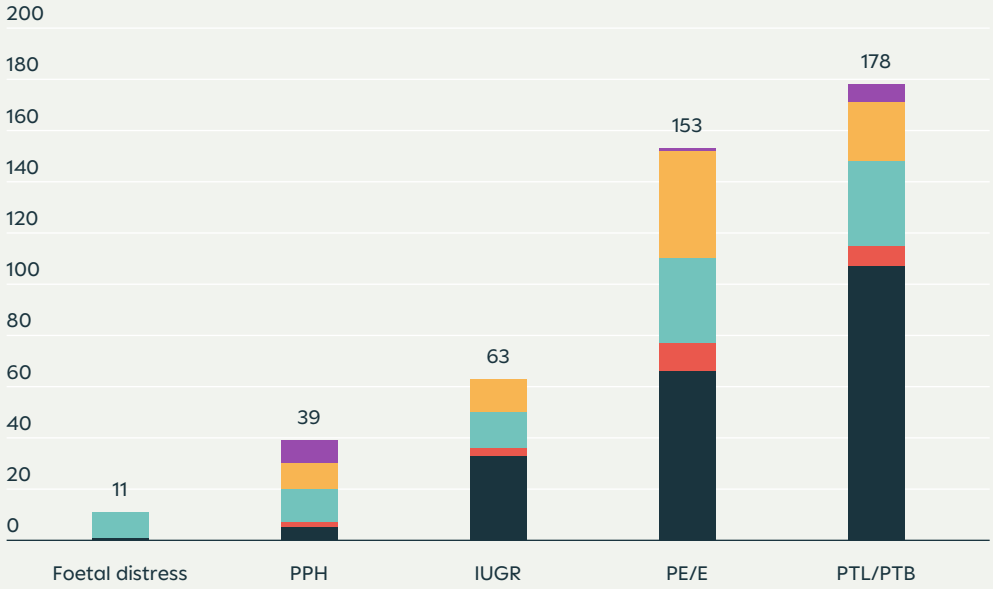
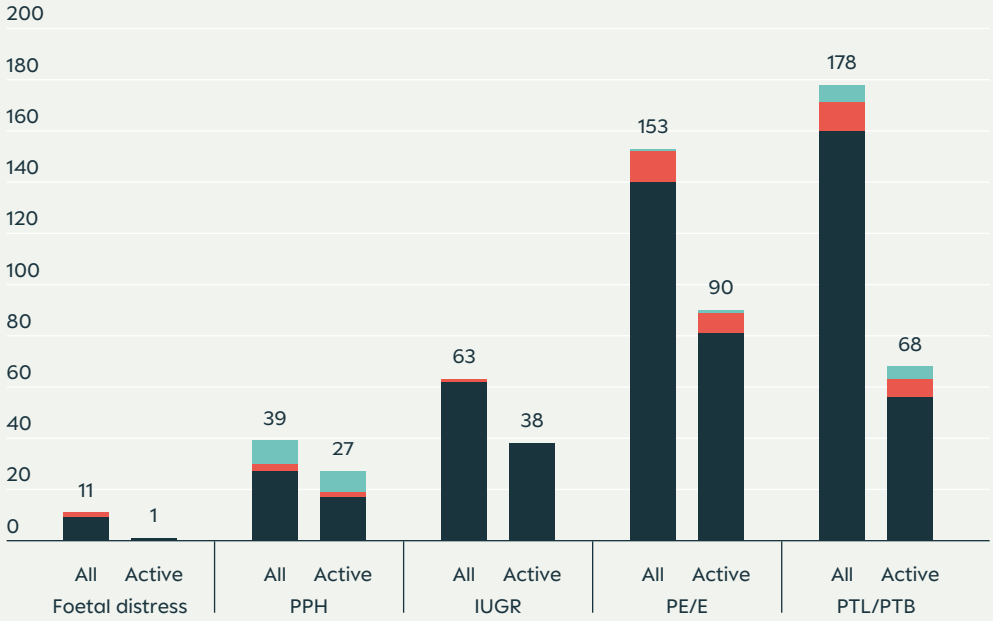


FIGURE 4
Number of candidates by clinical use status and by condition (all vs. active)

- Not yet aproved
- Used off label
- Approved/marketed



To assist with contextualising the landscape for these pregnancy conditions, we also reviewed the clinical use cases for each medicine (see Figure 4). Only 17 medicines (4%) we identified were approved and marketed for use across these five conditions. For PPH, these comprised a handful of effective but cold-chain and skilled-health-worker-dependent uterotonics, including the gold standard oxytocin as well as dinoprost, sulprostone, ergometrine/methylergometrine, oxytocin plus ergometrine in a fixed dose combination (i.e. syntometrine), carboprost, and carbetocin, alongside broader haemostatics like prothrombin complex concentrate and fresh frozen plasma (including cryoprecipitate) for treatment of severe haemorrhage, including PPH. Magnesium sulphate was the only approved drug for PE/E, indicated for the prevention and treatment of eclamptic seizures. There were seven approved medicines for PTL/PTB, including six tocolytics, which have been collectively mired by variable efficacy[28], notable side-effects (particularly for the betamimetics)[29], and/or controversy over endpoints and licensing.[30] These included hexoprenaline, isoxsuprine, fenoterol, ritodrine, allylestrenol, and atosiban. The seventh approved PTL/PTB medicine was for the prevention of PTL in women with a history of delivery prior to 35 weeks – injectable 17-alpha-hydroxyprogesterone caproate – although in 2020 the FDA recommended it be withdrawn from market due to lack of evidence of efficacy.[31] If this eventuates, it would effectively reduce indicated medicines for the prevention of PTL to zero. In sum, the arsenal to combat some of the greatest contributors to maternal mortality globally has its limitations.

It is therefore unsurprising that we identified documentation for 29 medicines (7%) that suggest routine off label use in clinical practice, the majority of which are therapeutic medicines for PE/E and PTL/PTB (e.g., a variety of antihypertensives used to manage preeclamptic/eclamptic hypertension, and a number of tocolytic drugs used to prolong gestation in women with PTL/PTB). While this reflects a necessity, it is disconcerting that clinicians and women continue to resort to medicines that have not previously been tested in controlled research environments for these conditions. The rest – the vast majority (398 candidates, 90%) – were not yet approved for clinical use, nor were they used off label. While this volume of candidates looks promising, more than half were in early discovery or preclinical (211 candidates, 53% of all not yet approved medicines), affirming that we are still some ways from converting this research into trialled and available medicines.

28
David M. Haas et al., 'Tocolytic Therapy for Preterm Delivery: Systematic Review and Network Meta-Analysis', *BMJ* 345 (9 October 2012): e6226, https://doi.org/10.1136/bmj.e6226.

29
James P. Neilson, Helen M. West, and Therese Dowswell, 'Betamimetics for Inhibiting Preterm Labour', *Cochrane Database of Systematic Reviews*, no. 2 (2014), https://doi.org/10.1002/14651858.CD004352.pub3.

30
Joshua D. Younger, Elena Reitman, and George Gallos, 'Tocolysis: Present and Future Treatment Options', *Seminars in Perinatology* 41, no. 8 (December 2017): 493–504, https://doi.org/10.1053/j.semperi.2017.08.008.

31
Center for Drug Evaluation and Research, 'Makena (Hydroxyprogesterone Caproate Injection) Information', *FDA*, 26 March 2021, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information.

PRETERM LABOUR/BIRTH

PTL/PTB represented the largest body of individual medicine candidates among the five conditions, totalling 178 (40%). Of these candidates, 132 (74%) were drugs, 14 (8%) were biologics, and 32 (18%) were dietary supplements. Overall, 68 candidates (38%) were being actively investigated and the remaining (110 candidates, 62%) were inactive. As a leading cause of perinatal morbidity and mortality and with numerous clinical avenues for intervention (including primary, secondary, and tertiary prevention measures; treatment; labour augmentation; etc.)[32], it is perhaps unsurprising that this condition dominated the field in terms of the volume of unique candidates investigated.

PTL also has a complex, and multifaceted pathology. Advances in our understanding of the condition's causes and progression have provided inroads to investigate new disease pathways and trial new molecules with preventive and therapeutic potential. For example, there are now numerous experimental drugs under investigation that target various stages of the known inflammatory cascade associated with PTL/PTB, including: toll-like receptor 4 antagonists (e.g. (+)-naxalone), cytokine suppressive anti-inflammatory drugs (e.g. OxZnI), NF-κs inhibitors (e.g. N-acetyl cysteine (NAC) and sulfasalazine), tumour necrosis factor alpha antagonists (e.g. etanercept), interleukin-1 receptor (IL-1) inhibitors (e.g. rytvela), as well as other anti-inflammatories such as omega-3 fatty acids and polyphenols.[33]

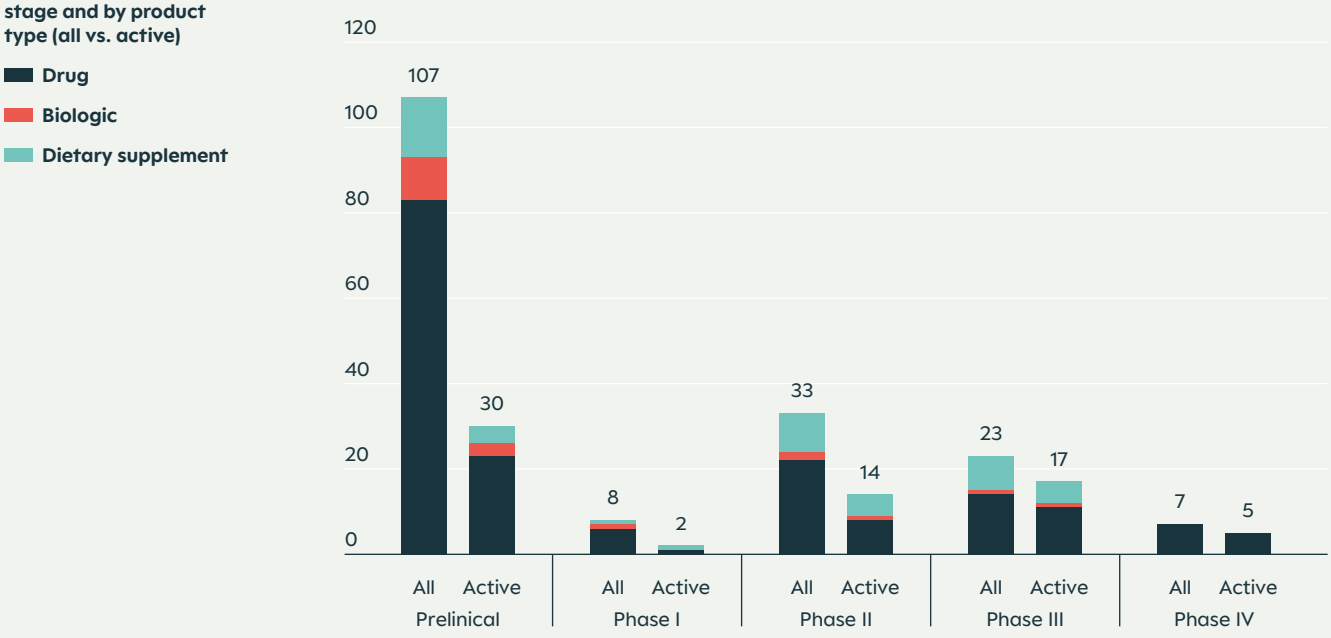
Early stage research was responsible for much of the volume of candidates that were not yet approved, which in total comprised 90% (160) of PTL/PTB candidates. Only seven candidates (4% of PTL medicines) were approved/marketed for this condition (mentioned above), with another 11 (6%) used off label (mostly tocolytics to prolong gestation in case of PTL, far downstream in the condition's disease progression). Within this landscape, there was a fairly even split by archetype, with 82 medicines (46%) NCEs and 96 (54%) repurposed.

Sixty percent (107) of PTL candidates were in preclinical development, 77 of which (72% of all PTL preclinical candidates) were inactive (see Figure 5). For only a handful of these inactive candidates (nine candidates in total) was there documented explanation for the discontinuation of research (e.g., adverse events, endpoints not met, recruitment issues etc.). Notable examples include issues with clinical trial recruitment and study design for promising oxytocin receptor antagonists retosiban (GSK) and nolasiban (ObsEva), which both halted Phase III and II trials due to protocol issues. The vast majority, however, have been classified as inactive due to a lack of recent updates. This may skew the overall dataset, as nearly a quarter of all candidates were for early stage PTL medicines research with no public updates from the three preceding years (2019 onwards), and were therefore assumed inactive.

32
Anca Matei et al., 'Primary and Secondary Prevention of Preterm Birth: A Review of Systematic Reviews and Ongoing Randomized Controlled Trials', *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 236 (May 2019): 224–39, https://doi.org/10.1016/j.ejogrb.2018.12.022.

33
Tegan Triggs, Sailesh Kumar, and Murray Mitchell, 'Experimental Drugs for the Inhibition of Preterm Labor', *Expert Opinion on Investigational Drugs* 29, no. 5 (May 2020): 507–23, https://doi.org/10.1080/13543784.2020.1752661.

FIGURE 5
Number of PTL/PTB candidates by R&D stage and by product type (all vs. active)



Active candidates in Phase II and III trials included a number of dietary supplements (ten candidates, 32%) investigated for their preventive effects on PTL, particularly for women identified as at risk. These included: omega 3 fatty-acids, vitamin B9, iron, vitamin D, zinc, magnesium, selenium, calcium, lycopene, and alpha-lipoic acid. Drugs in advanced stages of clinical development were comprised of a rich diversity of pharmacological classes under investigation, including progestins, vasodilators, antihypertensives, anti-inflammatory agents, anticholesteremic agents, antiemetics, etc. Of active drugs in clinical development, only one was a true NCE[34] – the prostaglandin F2 alpha antagonist ebopiprant (or OBE 022) – which is currently recruiting for Phase IIb/III trials. The developer ObsEva also recently announced its intention to explore an accelerated registration program of ebopiprant in Europe and to engage with the FDA for registration in the US.[35]

Of drug classes, progestins represented a significant body of active medicines R&D for PTL/PTB, and although the active compounds are similar, research around various formulations and routes of administration are quite distinct. Based on others' validation that route of administration is essentially a proxy for different types of progestogens[36], we decided to create separate entries based on this and other formulation distinctions. As such, the database includes several distinct entries for progesterone-based medicines for PTL/PTB, some of which are classified by route of administration (oral, injectable, and topical/vaginal). This reflects the diversity of applications of these medicines in clinical practice and is a distinguishing characteristic of how these are being investigated.

34
The other NCE is 17-alpha-hydroxyprogesterone caproate (oral), which is a new formulation of an existing medicine and is therefore not entirely novel in the sense it is meant here.

35
'ObsEva Presents PROLONG Phase 2a Proof-of-Concept Data on Ebopiprant (OBE022) for the Treatment of Spontaneous Preterm Labor at the RCOG Virtual World Congress 2021', *ObsEva* (blog), accessed 22 July 2021, https://www.obseva.com/pressrelease-detail/.

36
Jane E. Norman, 'Progesterone and Preterm Birth', *International Journal of Gynecology & Obstetrics* 150, no. 1 (July 2020): 24–30, https://doi.org/10.1002/ijgo.13187.

PREECLAMPSIA/ECLAMPSIA

PE/E represents a significant proportion of global perinatal morbidity and mortality, affecting up to 8% of pregnancies globally.[37] However, our understanding of its complex and inconsistent pathogenesis has only just begun to be unravelled. Similarly to PTL/PTB, this has resulted in multiple avenues for investigation from both preventative and treatment perspectives. As such, PE/E represented the next largest share of candidates, after PTL/PTB, at 153 (34% of all candidates captured). This figure consisted of 90 (59%) drugs, 25 (16%) biologics, and 38 (25%) dietary supplements. Overall, 90 (59%) candidates have been under recent active investigation, with the remaining (63 candidates, 41%) inactive.

One candidate – magnesium sulphate – is specifically indicated for PE/E, but only for prevention or treatment of eclamptic seizures, far downstream in disease presentation. Likewise, the 12 candidates used off label (8% of medicines) include several antihypertensives (ten) – e.g., labetalol, methyldopa, clonidine etc. – that form the mainstays in symptomatic treatment of preeclampsia-induced hypertension. The WHO recommend off label, prophylactic use of low-dose aspirin initiated before 20 weeks gestation to prevent preeclampsia in women at risk, but it is based on limited, albeit promising data.[38] Medicines that address the underlying cause of preeclampsia are currently elusive, but did comprise many of the remaining 140 candidates that were not yet approved but have been investigated for PE/E. Among the diverse avenues of R&D for PE/E were inflammation/immune modulators (e.g. sulfasalazine and celecoxib); angiogenic balancing medicines (e.g. biologics such as vascular endothelial growth factor, placental growth factor, etc.); vasoconstriction and vasodilation balancing drugs, such as nitric oxide donors or precursors (e.g. glyceryl trinitrate, sildenafil citrate) and hydrogen sulphide-based therapies (e.g. sodium hydrosulphide); proton pump inhibitors (e.g. esomeprazole); lipid lowering molecules/stains (e.g. pravastatin) and those targeting oxidative stress (e.g. melatonin, antioxidant vitamins, plant extracts etc.).[39,40,41]

37
Edgardo Abalos et al., 'Global and Regional Estimates of Preeclampsia and Eclampsia: A Systematic Review', *European Journal of Obstetrics & Gynecology and Reproductive Biology* 170, no. 1 (1 September 2013): 1–7, https://doi.org/10.1016/j.ejogrb.2013.05.005.

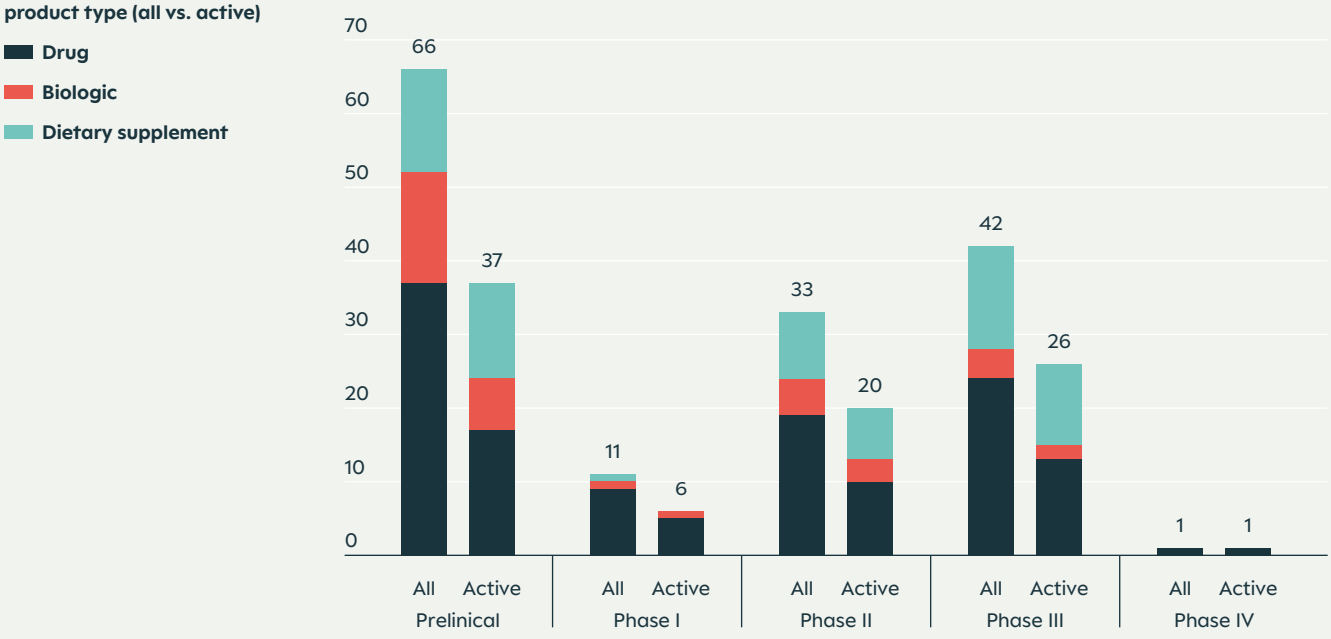
38
World Health Organization, *WHO Recommendations for Prevention and Treatment of Pre-Eclampsia and Eclampsia.*, 2011, http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf.

39
Charlotte J. Oyston, Joanna L. Stanley, and Philip N. Baker, 'Potential Targets for the Treatment of Preeclampsia', *Expert Opinion on Therapeutic Targets* 19, no. 11 (2015): 1517–30, https://doi.org/10.1517/14728222.2015.1088004.

40
Natasha de Alwis et al., 'Novel Approaches to Combat Preeclampsia: From New Drugs to Innovative Delivery', *Placenta* 102 (December 2020): 10–16, https://doi.org/10.1016/j.placenta.2020.08.022.

41
Stephen Tong et al., 'Pravastatin, Proton-Pump Inhibitors, Metformin, Micronutrients, and Biologics: New Horizons for the Prevention or Treatment of Preeclampsia', *American Journal of Obstetrics and Gynecology*, 16 September 2020, https://doi.org/10.1016/j.ajog.2020.09.014.

FIGURE 6
Number of PE/E candidates by R&D stage and by product type (all vs. active)



Thirty-eight (25%) PE/E candidates were NCEs, the lion's share of which (36 candidates, 95%) were in preclinical development. Many NCEs were also innovative biologics (15 candidates, 39% of NCEs), including cutting-edge siRNA-based therapies (e.g., soluble fms-like tyrosine kinase 1 (sFlt-1)-targeting siRNA, angiotensinogen (AGT)-targeting siRNA), as well as biologics with novel delivery mechanisms (e.g., VEGF-B via polypeptide delivery, Ad-VEGF via viral vector delivery, and haemoglobin-vesicles via nanoparticle delivery). Only half of all NCEs (19 candidates) were in active clinical development and only one NCE – a recombinant protein called RMC 035 (also commonly known as A1M-001, α1-microglobulin or ROSgard) – had advanced beyond preclinical trials and was in active Phase I clinical development. The remaining 115 (75%) were repurposed medicines, 75 (65%) of which reached Phase II or Phase III clinical trials. Forty-six repurposed drugs (30% of all PE/E medicines identified) were in active Phase II or Phase III at the time the database was finalised. This represented the largest body of active Phase II or III trials among any of the conditions (see Figure 6). However, it is important to note that 8 of these (17%) were already used off label for PE/E (mostly antihypertensives).

INTRAUTERINE GROWTH RESTRICTION

Foetal growth restriction can occur for many reasons, but the term IUGR as it is used here refers to its most common cause – uteroplacental insufficiency.[42] This pathology is shared with other placenta-mediated pregnancy conditions – namely PE/E – and as such the two conditions are intricately linked. This has both positive and negative implications. On one hand, recent improvements in our understanding of PE/E's pathogenesis have simultaneously provided critical insights into the disease processes and underlying causes of IUGR. It is no surprise then that IUGR candidates identified represented the third largest number of individual candidates after PE/E (63 in total), with over half (37 candidates, 59% of all IUGR candidates) shared between them, including a representative mixture of drugs, biologics, and dietary supplements. This is no doubt a useful R&D scenario. On the other hand, much of the shared R&D is primarily focused on PE/E and includes IUGR as a secondary outcome[43], with assumed benefits to the latter through amelioration of PE/E. This can make the results difficult to extrapolate definitively for IUGR.[44]

Nevertheless, there are some interesting (shared) avenues of research – some with dedicated focus to IUGR – that have translated into a number of innovative potential candidates in development. Of IUGR's total candidates, there were 30 (48%) drugs, 14 (22%) biologics, and 19 (30%) dietary supplements. At 22%, IUGR had the largest proportion of biologics investigated of the five conditions (although PE/E had the largest absolute number). Biologics under active investigation included Ad-VEGF in viral vector delivery, AGT-targeting siRNA, antithrombin, functional mitochondria therapy, insulin-like growth factor-1 in nanoparticle delivery, and VEGF-121.

Of all IUGR medicines, just under two thirds (38 candidates, 60%) were under active investigation, with the rest (25 candidates, 40%) inactive. This is promising, as there are currently no medicines that are approved for use for the treatment of IUGR, and only one of the 63 candidates (allylestrenol) was identified as being used off label for treatment of the condition[45] (however, although widely marketed, much of allylestrenol's use, availability and research appears to have been several decades ago). The remaining 62 candidates (98%) were not yet approved for use.

Consistent with the other conditions, medicines investigated for IUGR predominantly consisted of repurposed medicines (44 candidates, 70%). These comprised a number of dietary supplements (18 candidates, 41%) including a range of vitamins, minerals, herbs, omega-3 fatty acids, amino acids and polyphenols, but the majority were a diverse collection of repurposed drugs (23 candidates, 52% of repurposed candidates), including aspirin, heparins, statins (pravastatin), phosphodiesterase type 5 inhibitors (sildenafil and tadalafil), metformin and pentaerythrityl tetranitrate, amongst others.

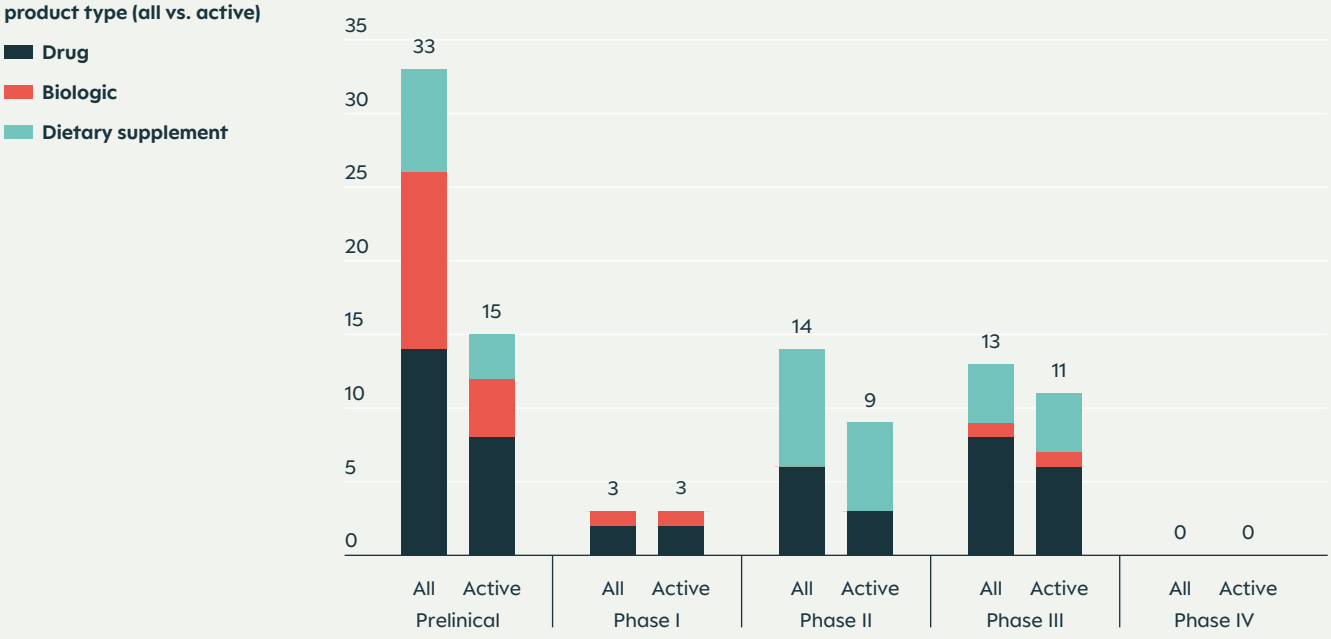
42
Katie M. Groom and Anna L. David, 'The Role of Aspirin, Heparin, and Other Interventions in the Prevention and Treatment of Fetal Growth Restriction', *American Journal of Obstetrics and Gynecology* 218, no. 2S (February 2018): S829–40, https://doi.org/10.1016/j.ajog.2017.11.565.

43
Some of this may be driven by challenges with correct prenatal diagnosis of IUGR (e.g., lack of sonographic equipment in resource-constrained settings, difficulty distinguishing a foetus that is actually growth restricted or just constitutionally small, or growth restricted for other reasons) and the complexity of measuring IUGR prevention or treatment as a primary outcome.

44
Groom and David, 'The Role of Aspirin, Heparin, and Other Interventions in the Prevention and Treatment of Fetal Growth Restriction'.

45
Narendra Malhotra and Ruchika Garg, 'Oral Allylestrenol: A Pregnancy-Supporting Progestogen', *Journal of South Asian Federation of Obstetrics and Gynaecology* 9, no. 4 (December 2017): 297–303, https://doi.org/10.5005/jp-journals-10006-1517.

FIGURE 7
Number of IUGR candidates by R&D stage and by product type (all vs. active)



The remaining 30% (19 candidates) were NCEs. Most were biologics (11 candidates, 58%) and nearly all the NCEs (18 candidates, 95%) were in preclinical development.

Indeed, the largest proportion of IUGR candidates only reached the preclinical stage (33 candidates, 52%). A total of 23 candidates were, however, in active development at Phase I, II, or III (see Figure 7). These include, for example, the only NCE in clinical development for IUGR – the maternal VEGF gene therapy candidate Ad-VEGF in viral vector delivery – which was in Phase I, as well as notable mid- to late stage sildenafil and tadalafil trials. Interest in sildenafil includes the international "Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction" (STRIDER) Consortium, comprised of five placebo-controlled randomised trials in the United Kingdom, New Zealand and Australia, The Netherlands, Canada, and Ireland. Unfortunately, the STRIDER trials were halted due to potential safety concerns with neonates (as well as futility) in some arms of the study.[46] Others reported no harm, but also no beneficial effect on growth.[47] The data is being reviewed in more detail, with the consortium recommending that in the meantime prescription of sildenafil for IUGR stops.[48]

46
Fieke Terstappen et al., 'Prenatal Use of Sildenafil in Fetal Growth Restriction and Its Effect on Neonatal Tissue Oxygenation—A Retrospective Analysis of Hemodynamic Data From Participants of the Dutch STRIDER Trial', *Frontiers in Pediatrics* 8 (3 December 2020): 595693, https://doi.org/10.3389/fped.2020.595693.

47
K. M. Groom et al., 'STRIDER NZAus: A Multicentre Randomised Controlled Trial of Sildenafil Therapy in Early-Onset Fetal Growth Restriction', *BJOG: An International Journal of Obstetrics and Gynaecology* 126, no. 8 (July 2019): 997–1006, https://doi.org/10.1111/1471-0528.15658.

48
K. M. Groom et al., 'Clinicians Should Stop Prescribing Sildenafil for Fetal Growth Restriction (FGR): Comment from the STRIDER Consortium', *Ultrasound in Obstetrics & Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology* 52, no. 3 (September 2018): 295–96, https://doi.org/10.1002/uog.19186.

POSTPARTUM HAEMORRHAGE

PPH is somewhat distinct from the rest of the conditions included in this project, with a quite different pathology and presentation. Defined as blood loss of 500mL or more within the first 24 hours after birth – caused largely by uterine atony, as well as birth canal trauma, retained placental tissue or impaired haemostasis/maternal bleeding disorders[49] – it could arguably be described as a more mechanical complication. As such, we saw a markedly different type of R&D landscape and quantum of medicines for this condition. This comprised 39 candidates, over half of which (22 candidates, 56%) were drugs (including a number of oxytocics/uterotonics), five (13%) biologics (all haemostatics and coagulants), and 12 (31%) dietary supplements (mostly traditionally used herbs). It's worth noting the broader PPH R&D landscape does include a number of effective devices, such as balloon[50] or vacuum-induced[51] uterine tamponades, but this is outside this project scope and they were therefore not included.

Overall, 27 medicines candidates (69%) were being actively investigated for PPH – the largest proportion of active candidates of the five pregnancy-related conditions – with the remaining 12 (31%) inactive. A third of all PPH medicines (13 candidates, 33%) were also NCEs – the second highest proportion after PTL/PTB – with the remaining repurposed medicines (26 candidates, 67%). What these figures obscure, however, is that nearly a third (8 candidates, 30%) of active candidates and almost half (six candidates, 46%) of NCEs were already approved and indicated for use in PPH. In fact, almost a quarter (nine candidates, 23%) of all PPH candidates were already approved for use, with another three (8%) identified as being used off label. Furthermore, the nine approved PPH medicines constituted over half (53%) of all approved medicines identified across the five conditions (17 candidates in total). Some of these – including the three haemostatic agents desmopressin, fresh frozen plasma and prothrombin complex concentrate (the latter two being the only approved biologic medicines across the five conditions) – reflect the fact that haemorrhage is, of course, a complication not unique to pregnancy. This nuance needs highlighting here: that medicines to address haemorrhage of any type that were also reported as medicines for PPH were classed as approved.

49
Joshua P. Vogel et al., 'WHO Recommendations on Uterotonics for Postpartum Haemorrhage Prevention: What Works, and Which One?', *BMJ Global Health* 4, no. 2 (2019): e001466, https://doi.org/10.1136/bmjgh-2019-001466.

50
'Uterine Balloon Tamponade for the Treatment of Postpartum Hemorrhage: A Systematic Review and Meta-Analysis – PubMed', accessed 1 April 2021, https://pubmed.ncbi.nlm.nih.gov/31917139/.

51
Mary E. D'Alton et al., 'Intrauterine Vacuum-Induced Hemorrhage-Control Device for Rapid Treatment of Postpartum Hemorrhage', *Obstetrics and Gynecology* 136, no. 5 (November 2020): 882–91, https://doi.org/10.1097/AOG.0000000000004138.

Having said that, most of the approved candidates were uterotonics expressly indicated for PPH (and other conditions related to uterine contraction, such as miscarriage, abortion and labour induction), including a range of oxytocin and oxytocin analogues, prostaglandins and ergot alkaloids that are effective and have been available for some time. What this reflects is that many approved PPH medicines – while highly effective – are suboptimal for use in a variety of contexts, particularly low-resource, LMICs. This is comparable perhaps to the contraceptive R&D landscape, where a reasonable amount of highly effective options exist but they are not always fit for purpose for the many populations impacted, leaving much room (and need) for continued improvement or new products altogether. This is particularly pertinent given PPH affects 5% of all pregnancies worldwide, is responsible for nearly a quarter of all maternal deaths globally, and is the leading cause of maternal mortality in most LMICs.[52]

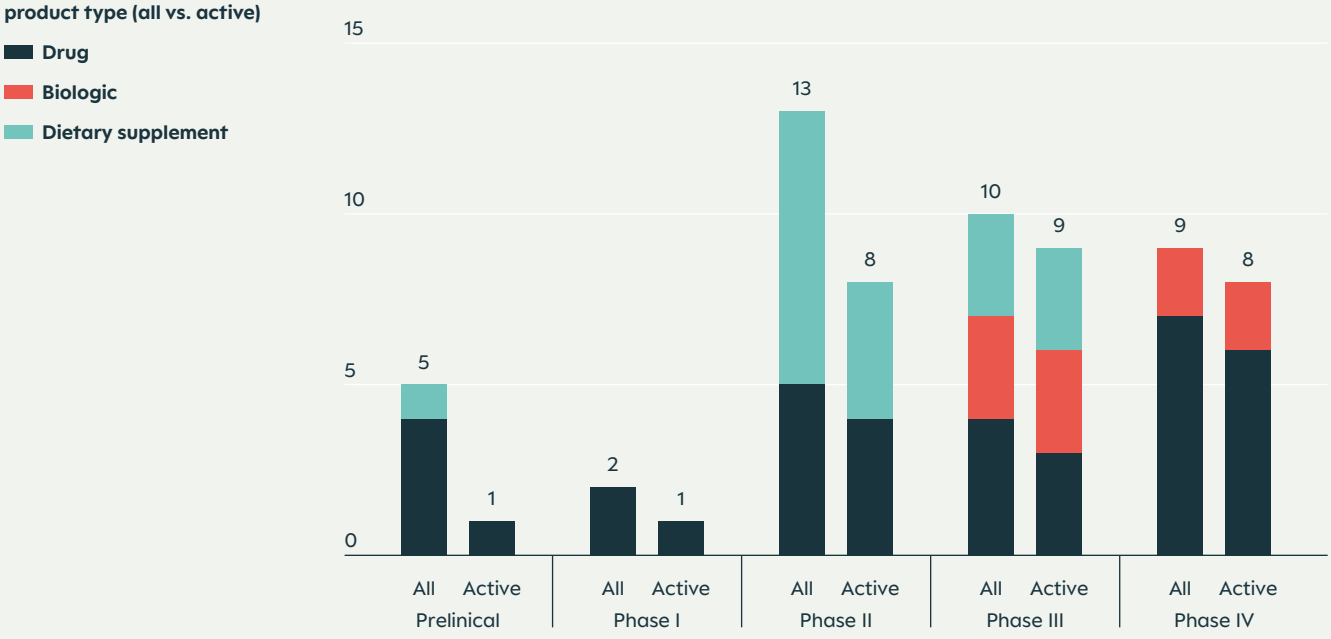
Unsurprisingly therefore, the remaining 27 PPH candidates (69%) that were not yet approved included a number of candidates in development that were specifically designed with LMICs in mind. This included seven NCEs, many of which are reformulations of tried and effective uterotonics, such as oxytocin in a subcutaneous uniject device; sublingual, orally disintegrating oxytocin; inhalable, heat stable oxytocin; and heat stable carbetocin. Only the latter two, however, were active. Despite oxytocin in uniject completing trials with positive outcomes, there has been little progress on its roll out, while Phase I trials of Oxytone Bioscience's orally disintegrating oxytocin were terminated due to protocol issues. However, heat stable carbetocin has recently completed one of the largest global PPH prevention trials – the CHAMPION (Carbetocin Haemorrhage Prevention) trial, a unique partnership project between the WHO, MSD for Mothers and Ferring Pharmaceuticals – with positive results.[53] In May 2020, Ferring received approval for heat stable carbetocin from Swissmedic through its new *Marketing Authorisation for Global Health Products (MAGHP)* procedure. National regulatory approval procedures are underway in target demonstration markets (India, Kenya, and Nigeria) and it is likely that relatively soon it will join the list of medicines fully marketed, approved, and available for PPH.[54]

52
World Health Organization, 'WHO Recommendations: Uterotonics for the Prevention of Postpartum Haemorrhage', 2018, https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1.

53
Mariana Widmer et al., 'Heat-Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth', *New England Journal of Medicine* 379, no. 8 (23 August 2018): 743–52, https://doi.org/10.1056/NEJMoa1805489.

54
'The_champion_project_teaching_case_2020_12_02.Pdf', accessed 23 July 2021, https://www.globalhealthdelivery.org/files/ghd/files/the_champion_project_teaching_case_2020_12_02.pdf.

FIGURE 8
Number of PPH candidates by R&D stage and by product type (all vs. active)



The unique landscape of PPH R&D is reflected in the candidate R&D stages, with the largest number (and proportion) of candidates reaching Phase IV trials of any condition (a reflection of the relatively high volume of approved candidates). There were only seven candidates in early stage development (preclinical or Phase I), only two of which were active (propranolol and inhaled heat stable oxytocin, the latter still active despite GSK returning the rights to the product to Monash University, who are continuing its development). The majority (23 candidates, 59% of all PPH candidates) had reached Phase II or Phase III trials, and 17 (74%) of these were in active development (see Figure 8). There was only one active NCE in Phase III – heat stable carbetocin – which as noted is progressing to registration. The remaining Phase III candidates were repurposed medicines, including, some promising trials using the antifibrinolytic agent tranexamic acid for treatment of PPH.

INTRAPARTUM FOETAL DISTRESS

Among the five conditions, foetal distress had the smallest body of medicines research and development recorded in the last 20 years. The urgent nature of the condition – hypoxia induced intrapartum foetal distress usually detected by an abnormal foetal heart rate during labour – often leaves little time to intervene medically after diagnosis. Options investigated are largely not medicine-based, and include maternal hyperoxygenation, maternal repositioning, amnioinfusion and IV fluid administration[55]. In severe cases, immediate delivery remains the preferred clinical management strategy. This urgency adds an element of complexity to investigating novel medicine candidates for treatment of this condition. Moreover, risk factors for foetal distress include, amongst others, PE/E and IUGR[56], and it is here where research focus and prioritisation remain.

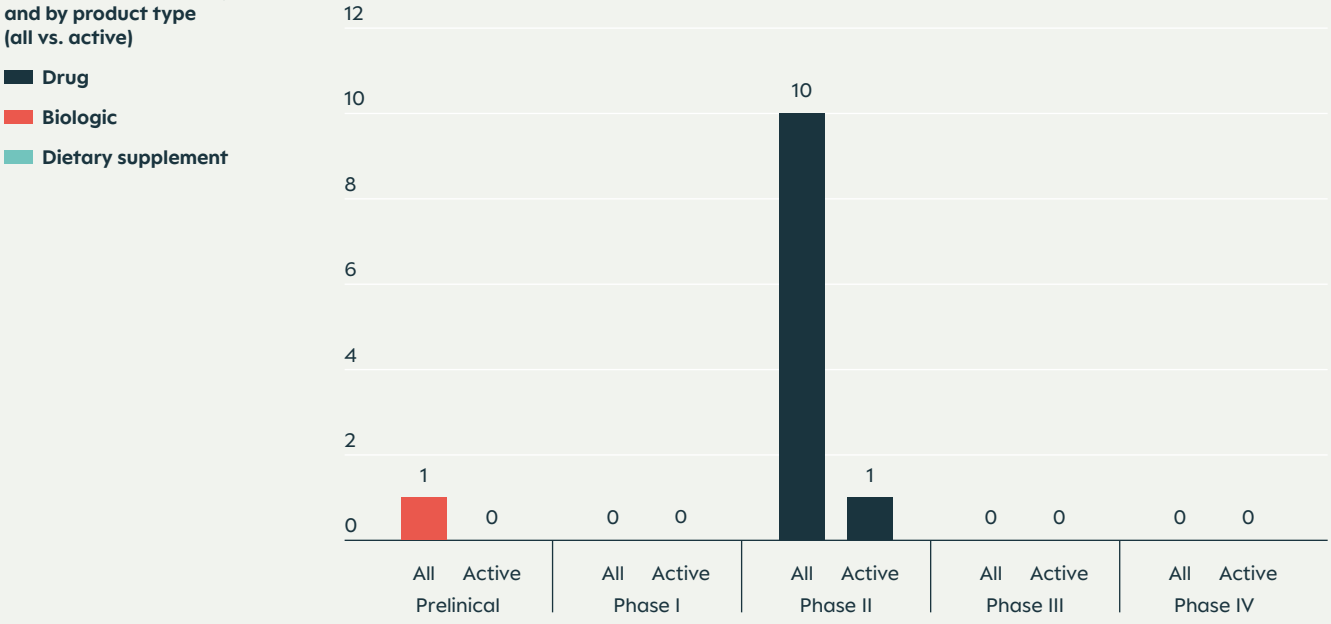
It was not a surprise therefore that in total there were just 11 candidates investigated with indications for foetal distress. None of these included already approved medicines, as none yet exist for management of this condition. Of the total, ten (91%) were drugs, all of which were repurposed. Eight of the ten drugs (80%) were tocolytics aimed at reducing uterine contractions (including incidence of tachysystole), and therefore improving placental circulation and foetal oxygenation.[57]

55
Lauren M. Bullens et al., 'Interventions for Intrauterine Resuscitation in Suspected Fetal Distress During Term Labor: A Systematic Review', *Obstetrical & Gynecological Survey* 70, no. 8 (August 2015): 524–39, https://doi.org/10.1097/OGX.0000000000000215.

56
Lauren Bullens, *Management of Fetal Stress during Term Labor* (S.l.: s.n., 2018), https://pure.tue.nl/ws/files/114197316/20181221_Bullens.pdf.

57
Sebastian J. Leathersich et al., 'Acute Tocolysis for Uterine Tachysystole or Suspected Fetal Distress', *The Cochrane Database of Systematic Reviews* 7 (4 July 2018): CD009770, https://doi.org/10.1002/14651858.CD009770.pub2.

FIGURE 9
Number of foetal distress candidates by R&D stage and by product type (all vs. active)



Although all tocolytics under investigation were inactive, two – salbutamol and terbutaline, both beta-adrenergic agonists – remain part of many national and international guidelines for the management of foetal distress in labour, and are regularly/actively used off label for this indication.[58,59] All other foetal distress medicines (nine candidates, 82%) were not yet approved.

Outside drugs, the remaining candidate was a single biologic (9%) – haemoglobin vesicles in nanoparticle delivery – which was also the only NCE in development. However, preclinical work on this innovative nanotechnology-based therapy is a way off being translated to an available therapy, was largely focused on PE/E and IUGR, and was, in any case, inactive. There were no dietary supplements investigated for foetal distress within the past 20 years that we found. Only one foetal distress candidate – sildenafil citrate – was under active investigation. The 2020 RIDSTRESS ("Reducing the Incidence of Fetal Distress with Sildenafil Citrate") study demonstrated promising results, although the authors noted that larger trials are needed before its use can be recommended in cases of foetal distress.[60] All of the remaining ten (91%) candidates were inactive, having halted at Phase II trials (see Figure 9).

58
Elizabeth Ayebare et al., 'Health Care Workers' Experiences of Managing Foetal Distress and Birth Asphyxia at Health Facilities in Northern Uganda', *Reproductive Health* 18, no. 1 (5 February 2021): 29, https://doi.org/10.1186/s12978-021-01083-1.

59
'RANZCOG – Intrapartum Fetal Surveillance Clinical Guideline Updated', accessed 27 July 2021, https://ranzcog.edu.au/news/intrapartum-fetal-surveillance-clinical-guideline.

60
Jessica Turner et al., 'Safety and Efficacy of Sildenafil Citrate to Reduce Operative Birth for Intrapartum Fetal Compromise at Term: A Phase 2 Randomized Controlled Trial', *American Journal of Obstetrics and Gynecology* 222, no. 5 (May 2020): 401–14, https://doi.org/10.1016/j.ajog.2020.01.025.

IV DISCUSSION

Given the paucity of R&D into maternal health medicines demonstrated in Fisk and Atun's 2008 paper, and the lack of new products on the market since then, the general hypothesis at the outset of this undertaking was that the volume of candidates uncovered would potentially be similarly small. As such, even despite the differences in scope and methodologies, the comparably large number of candidates identified here was unexpected.

Rejuvenated interest in these issues should be lauded. However, looks can be deceiving, and the data presented here requires additional analysis to put it in context. Foremost, while the body of research looks sizeable, about half of all identified candidates were inactive (220 candidates, 49.5%). In addition, just under half of all candidates were preclinical (212 candidates, 48%), either not yet or never having made it to clinical trials. A broad field of preclinical R&D is no doubt positive. However, given the lengthy time it takes for medicines to proceed from initial development through to market launch, any active candidates being investigated now at early stage (83 candidates, 39% of preclinical candidates) – even assuming they show promise – are some way off being available and utilised.

Nonetheless, there were also 63 candidates that were both active and in late stage, Phase III clinical trials, the highest number of active candidates in any phase outside of preclinical. This looks extremely encouraging but is worth breaking down. Just under a quarter of these (15 candidates, 24%) were already used routinely off label for that condition, and of the remaining 48, there were only seven biologics and 18 drugs. There was also variability within these candidates' clinical progression, including some with results published recently but not seemingly active anymore, as well as some with mixed or not particularly positive results. There was also wide variability in indication, including those looking at prevention in at risk groups, intervention at specific stages of the condition, symptomatic treatment, as well as working upstream on the condition's underlying pathogenesis. In short, caution is warranted when conflating these candidates into a single figure, as it probably doesn't represent a large, homogenous stash of 'cures' for these conditions on the edge of approval (and indeed none at all were active and in Phase III for foetal distress).

Moreover, of all active Phase III candidates, only one – heat stable carbetocin for PPH – was a new product/NCE (albeit a reformulation of carbetocin, and only for prevention not treatment of PPH), with all the rest repurposed medicines or ones already used off label. Repurposed and off label medicines use – as seen across conditions in this database – is not an uncommon trend in pregnancy-related clinical practice and R&D. As noted by Fisk and Atun, it is both a product of, and does little to stimulate interest in, already limited investment in R&D, particularly for entirely new products.[61] With two thirds of the entire landscape (and just under three quarters of active candidates) being repurposed medicines, our data confirms this is still a relevant issue, and perhaps elevates interest in the 58 active NCE candidates in development as we scan the horizon for potentially new, transformative maternal medicines for the future.

Interestingly, of the ten active PTL/PTB and three active PE/E candidates identified by Fisk and Atun in 2007[62] – most of which were NCEs – only two are still in active development: injectable 17-alpha-hydroxyprogesterone caproate/17-OHCP (makena, previously gestiva) and vaginal progesterone (including crinone, utrogestan etc). Injectable 17-OHCP was approved by the FDA in 2011 for prevention of PTL in at-risk women, while vaginal progesterone is widely used off label for prevention of PTL in women with a short cervix (the brand medicine utrogestan has been marketed for prevention of PTL, but does not appear to be widely recommended for its use, instead largely marketed for assisted reproductive technology (ART) cycle support).[63] Both, however, are muddied by controversy, with major long-term clinical trials demonstrating questionable efficacy, effectively culminating in the 2020 FDA request for makena's withdrawal from the market.

The rest, however, are now inactive. Tellingly, these include a number of promising candidates that had progressed, only to be terminated at a more advanced stage due to recruitment and study design issues. Among these were the novel oxytocin receptor antagonist 221149 (retosiban[64]) and all three PE/E candidates relaxin (serelaxin), digibind and digoxin antibody (both under the single candidate AMAG 423), despite the latter being granted orphan drug status[65] for treatment of severe PE/E by the FDA in 2012. Even nolasiban – which likely superseded or is a continuation of AS-602305 in Fisk and Atun's paper – terminated its Phase II research due to enrolment difficulties. Shared key issues include the problem of a small study population, difficulty with diagnostic consensus, and the ethics of (and resistance to) use of a placebo comparator. Clinical development involving pregnant women, and for these largely complex yet serious conditions, is clearly problematic.

61
Fisk and Atun, 'Market Failure and the Poverty of New Drugs in Maternal Health'.

62
Fisk and Atun identified 17 active candidates: ten for PTL/PTB ('labour inhibition'); two for PE/E ('preeclampsia'); one for PE/E and 'labour induction'; two for 'labour induction' and two for 'miscarriage'. Only PTL/PTB and PE/E are pregnancy-related conditions that are part of our scope, and therefore only candidates with these indications were available for comparison.

63
'Products', accessed 27 July 2021, https://www.besins-healthcare.com/products/.

64
Candidate names here in brackets refer to the equivalent candidate in our database.

65
Orphan drug status is a designation granted (upon application) to certain drugs or biologics to treat rare diseases or conditions where little commercial incentive for their development exists. The status offers development benefits such as tax credits and fee waivers etc. See https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products.

FIGURE 10
Number of active clinical trials for each pregnancy-specific condition in a given year (2000-2020)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Foetal distress	1	2	1	4	5	4	3	2	0	0	0	0	0	0	0	1	1	1	1	1	1
IUGR	2	2	4	6	5	8	11	6	7	6	6	8	14	16	26	28	25	28	24	23	22
PPH	1	1	4	3	3	10	13	18	19	27	39	37	52	63	66	84	94	77	85	100	100
PE/E	5	7	10	15	24	30	27	22	24	25	26	32	43	49	60	76	79	74	103	106	105
PTL/PTB	5	14	15	25	38	41	52	56	66	64	63	68	83	82	82	96	118	142	124	99	103

Despite this, the landscape does give a clear indication that there has been some growing interest and investment in maternal health medicines R&D over time – from both the large volume of preclinical R&D now captured (compared with Fisk and Atun), as well as what appears to be a surge of energy and interest in clinical development in some of the conditions over the last decade (see Figure 10). Although clinical trial data has been largely retrieved from WHO's ICTRP (which has its own limitations, including a potential reporting bias that may have arisen from improved compliance with and utilisation of the database over the period investigated), Figure 10 nonetheless demonstrates at a macro level the increased frequency of clinical activity related to these pregnancy-related conditions over time, as well as signalling where and when R&D has (or hasn't) built momentum. Although this does not provide insight into the quality of trials or candidates in play, it does reflect interest and investment, which is encouraging.

Documenting medicines in development for these conditions has also illustrated a broad diversity of pharmacological classes and subgroups under investigation. This is particularly true for PTL/PTB, PE/E and IUGR, where a number of intervention points within a complex, but progressively demystified pathology has translated to numerous potential preventive and therapeutic targets. The result is myriad research trajectories and candidates in motion – some novel, most repurposed, and many at early stage. While this mushrooming field of investigative R&D will be critical to fill the current product gaps for these conditions, the portfolio is not yet led by any unified agenda. Medicines development for other global health issues, such as tuberculosis, malaria, HIV, neglected diseases and global antimicrobial resistance, have benefited considerably from dedicated and coordinated push-pull mechanisms to advance products forward. Given how difficult it is to move even the most promising products through the maternal health pipeline, it seems accelerated progress is unlikely to be made unless there is a sector-wide, coherent action plan to do so.

ANNEXE 1
FIELD DEFINITIONS AND GUIDANCE NOTES

Data field	Definition	Data input type	Data example	Additional guidance notes
Candidate entry				
Candidate ID	Three-digit unique identifier of candidate, assigned internally by PCR.	Numeric	e.g., 123	N/A
Candidate name	The current candidate name, or if not active, the name it had at the time it was last active. International non-proprietary (generic) name if available.	Free text	e.g., aspirin	If a candidate is investigated for more than one of the five pregnancy-related conditions, that candidate should be entered more than once, with a signifier in the name (e.g., 'aspirin – PE/E', 'aspirin – PTL/PTB' etc.)
Alternative/previous candidate names	Any other previous names the candidate has had or been referred to as.	Free text	e.g., acetylsalicylic acid; ASA	N/A
Pregnancy-specific condition (primary)	Which of the five pregnancy-specific conditions the candidate is focussed on treating or preventing for this entry.	Drop-down (list)	e.g., Preterm labour/birth (PTL/PTB); Preeclampsia/eclampsia (PE/E); Intrauterine growth restriction (IUGR); Postpartum haemorrhage (PPH); Foetal distress	If the candidate is investigated for more than one of the five pregnancy-related conditions, that candidate should be entered more than once, with a signifier in the name. (e.g., 'aspirin – PE/E', 'aspirin – PTL/PTB' etc.)
Indication	Within the pregnancy-specific condition, the sub-category of focus of the candidate.	Free text	e.g., 'management of early onset preeclampsia'; 'treatment of eclampsia (eclamptic seizures)', 'prevention of PPH', 'delay of labour/birth' etc.	N/A
Archetype	What sub-category of product the candidate represents, specifically whether it is repurposed or a new chemical entity.	Drop-down (list)	e.g., new chemical or biological entity; Repurposed	Repurposed' candidates are any candidate previously or currently marketed for any other condition. 'New chemical or biological entities (NCEs)' are candidates not already marketed for any condition, unless it is an NCE marketed for that specific pregnancy-related condition (e.g., under PTL, atosiban is an NCE as it was developed and now marketed for PTL, whereas under foetal distress, atosiban is a repurposed drug, as it is already marketed for another condition (PTL)).

Data field	Definition	Data input type	Data example	Additional guidance notes
Candidate entry				
Product type	Whether the candidate is a drug, biologic, or dietary supplement. Drugs are defined as small molecules, usually chemically synthesised; biologics as large complex molecules, derived from animals /humans/ microorganisms, usually via biotechnology; and dietary supplements according to the US FDA definition.	Drop-down (list)	e.g., Drug; Biologic; Dietary supplement	Dietary supplements are broadly defined following the US FDA definition (https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements), but tailored for functionality and usability, e.g. keep specific groupings of compounds together, such as polyphenols (some of which may border on drugs). For inclusion, dietary supplements need to be dosed formulations (i.e., food-based interventions such as 'beetroot juice' or 'chocolate' alone are not considered in scope). Dietary compounds specifically registered as a drug (e.g., N-acetyl cysteine), and others that are specific chemical isolates originally from dietary sources (e.g., carveol) are drugs.
WHO ATC code	The candidate's exact WHO ATC drug class code and description (if available).	Free text	e.g., H01BB02 (for oxytocin)	If not available, write N/A.
Medical subject headings	The candidate's related NIH Medical Subject Headings, listed under the "Pharm Action". If not available, other keywords to describe the pharmacological or therapeutic uses for the candidate.	Free text	e.g., Oxytocics; Uterotonics (for oxytocin)	The MIH MeSh website is (https://meshb.nlm.nih.gov/search). Other useful keywords that describe the pharmacological or therapeutic uses for the candidate can be found through other websites or literature. e.g., for terbutaline, these might be 'Bronchodilator agents; Sympathomimetics; Tocolytic agents; Adrenergic beta-2 receptor agonists'
Pharmacological subgroup	The candidate's WHO ATC 4th level classification or FDC EPC classification.	Free text	e.g., Oxytocin and analogues (i.e., H01BB for oxytocin)	If not available, write N/A.
Route of administration	How the medicine is administered or taken.	Free text	e.g., inhaled; nasal; oral; sublingual; rectal; subcutaneous; transdermal; intramuscular; intravenous; intra-umbilical; intra-amniotic; etc.	If unknown, as is likely with some preclinical candidates, write 'unknown'.
Target	Pharmacological target the candidate acts on.	Free text	e.g., 'epidermal growth factor receptor (EGFR) pathway', '3-hydroxy-methylglutaryl coenzyme A reductase pathway'; 'hypoxia-inducible factor-1 alpha (HIF-1a)', etc.	If unknown, write 'unknown'.

Data field	Definition	Data input type	Data example	Additional guidance notes
Candidate entry				
Mode of action	A description of how the medicine works.	Free text	e.g., 'Oxytocin receptor agonism leads to an increase in myometrial tone and muscle contraction'	If unknown, write 'unknown'.
Clinical use status	Whether the candidate is purely investigational/ not yet approved, already approved/ marketed, or used off label for that condition.	Drop-down (list)	e.g., 'Approved/marketed; Used off label; Not yet approved	N/A
Current R&D stage for this pregnancy condition	The current R&D stage of the candidate for the specific pregnancy-related condition specified above. If not active, the R&D stage the candidate was at for the condition when it stopped being active.	Free text	e.g., 'Preclinical, 'Phase II', 'Phase IIb/III', 'Phase III'; 'Phase IV'	To allocate a single, appropriate R&D stage to each candidate, review linked clinical trials against accepted definitions of each R&D stage (preclinical through to Phase IV), and assign a phase based on trial descriptions. NB Only candidates already marketed for that condition can be labelled Phase IV.
Highest R&D stage for any condition	The highest R&D stage reached for the candidate for or any condition or indication.	Free text	e.g., 'Phase II (Preeclampsia); Approved (Stroke)'.	N/A
Development status	Whether the candidate's development is active or inactive.	Drop-down (list)	e.g., Active; Inactive	Active candidates must have evidence of R&D within the last three years (since 2019). If no updates available in the previous three years, or there is clear evidence of their discontinuation since then, mark as inactive.
Inactive development type	If development status is inactive: A broad classification of reason as to why development of the drug is inactive for the pregnancy specific condition.	Drop-down (list)	e.g., Funding issues'; Study design/ recruitment/ethics issues; Endpoints not met; Adverse events; Other; N/A	If the reason is due to no recent updates since 2019, select 'Other'.
Inactive development reason	A more detailed reason for why development is inactive.	Free text	e.g., 'R&D abandoned because of increased incidence of cardiac arrhythmias in intervention arm (adverse events)'	If the reason is due to no recent updates since 2019, write 'No recent updates'.

Data field	Definition	Data input type	Data example	Additional guidance notes
Candidate entry				
Key features/ challenges	Concise description of the candidate information, in a prescribed format.	Free text	e.g., Carbetocin, sold under the brand names Pabal or Duratocin among others, is a long-acting synthetic analogue of oxytocin that was developed for the prevention of labour disorders like uterine atony and excessive postpartum haemorrhage following caesarean section. Its indication has since been extended to use with vaginal delivery. Carbetocin is administered as a single 100 µg/mL intravenous injection (and also intramuscularly) before or after placental delivery which is sufficient to maintain adequate uterine contraction. It is proposed to have advantages over oxytocin in the management of third-stage labour. Like oxytocin, carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus; this stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterus musculature. Carbetocin can increase the rate and force of spontaneous contractions of the postpartum uterus. Onset of action is rapid with a firm contraction achieved within 2 minutes. Carbetocin has the potential to be a near ideal drug for routine PPH prophylaxis, offered in all hospital vaginal deliveries, because it is suitable for both intramuscular injection and intravenous administration, offering convenience and simple implementation; it has quick onset of action; is long-acting, especially compared to oxytocin (carbetocin has a half-life of 85-100 minutes with a more prolonged uterotonic effect compared with endogenous or synthetic oxytocin's half-life of 3.5min); is rarely associated with adverse drug reactions; and has excellent tolerability.	Descriptions should include general information on the candidates and how it works; any relevant history of its development; and any positive or negatives/challenges of the drug (e.g., side effects), as appropriate.
Most recent update	Concise description of latest update – if appropriate.	Free text	e.g., As of April 2020, Phase II trials in the UK and Australia were discontinued, and GlaxoSmithKline returned the rights related to inhaled oxytocin back to Monash University.	Adis Insight already provided information on key recent update (if listed there).
FDA pregnancy labelling/pregnancy risk summary	Candidate's FDA pregnancy label (if approved) or pregnancy risk summary (if not yet approved).	Free text	No drug systemic absorption; Risk statement based on human data; Risk statement based on animal data; Risk statement based on pharmacology; Background risk information in general population; Background risk information in disease population	Information available on FDA drug labels. If not approved (i.e., not available), write 'N/A'.

Data field	Definition	Data input type	Data example	Additional guidance notes
Candidate entry				
Preclinical results status	Have results been published (any format).	Drop-down (list)	e.g., Results available; Results not available; Unknown; N/A	N/A
Preclinical results type	Nature of publication. Include whichever is the most recent or 'meaningful'.	Drop-down (list)	e.g., Press release; Conference abstract presentation; Preprint article; Peer reviewed article; Government document; Other; N/A	N/A
Preclinical results source	URL link to published source, preferably PubMed URL. Include whichever is/are the most recent or meaningful.	Hyperlink	e.g., https://pubmed.ncbi.nlm.nih.gov/15185220/	PubMed URL if available.
Investigated for other indications	Whether the candidate has ever been investigated for any other indication or condition.	Drop-down (list)	e.g., Yes; No	This includes any conditions for which it is already marketed.
Other indications	Concise descriptions of any other condition or indication the candidate has been investigated for, and any context (if yes to above field).	Free text	e.g., 'Hypertension; Stroke; Cancer.'	This includes any conditions for which it is already marketed.
Developers	List of key organisations involved in the candidate's development. This includes current developers, originators, Universities; patent owners etc.	Free text	e.g., 'Novartis; Monash University'	Include all relevant organisations. For organisations in preclinical, include Universities. If off-patent, include 'off-patent'.
Patent	Patent number or code as per patent database (where available)	Free text	e.g., EP2621468B1	Can be found in Adis, PubChem or Drugbank etc.
CAS number	Candidate's CAS number	Free text	e.g., 68-96-2	Can be found in Adis, PubChem or Drugbank etc.
Chemical name	IUPAC chemical name in words	Free text	e.g., trans-4-(aminomethyl) cyclohexane carboxylic acid (for tranexamic acid)	Can be found in Adis, PubChem or Drugbank etc.

Data field	Definition	Data input type	Data example	Additional guidance notes
Clinical trial entry				
CT title	Exact title as it appears from the source.	Free text	e.g., 'A Single Centre, Single Blind Study to Investigate the Safety, Tolerability and Pharmacokinetics of Single Doses of Oxytocin (GR121619) Administered Via an Inhaled Route in Healthy Female Volunteers'	This may differ slightly between sources.
CT number	Unique CT identifier as per CT database. If more than one, list all separated by semi-colons.	Alpha-numeric	e.g., NCT04368728	If the CT is relevant to more than one candidate in the database, duplicate CT entries should be made, and assigned it to the additional/other candidate/s.
CT last updated	CT last updated date as per CT database. Date written as dd/mm/yyyy.	Free text	e.g., 21/03/2021	If unknown, write 'unknown'.
CT phase	CT stage/phase as per CT database.	Free text	e.g., Phase II	Write exactly as presented. For those that say 'N/A' or 'unknown', write 'N/A' or 'unknown'. Include specifics such as 'Phase IIb'
CT source	Link to clinical trial record.	Free text	e.g., https://clinicaltrials.gov/ct2/show/NCT005495	These links can be found in the 'web address' column of the ICTRP data sets. Otherwise the URL where sourced.
CT status	CT status as per CT database.	Drop-down (list)	e.g., Planned; Recruiting; Active; Completed; Terminated; Unknown; Withdrawn; Not yet recruiting; Active, not recruiting; Enrolling by invitation; Suspended	N/A
CT terminated type	If CT status is terminated: A broad classification of reason as to why development of the trial was terminated	Drop-down (list)	e.g., Funding issues; Study design/ recruitment/ethics; Endpoints not met; Adverse events; Unknown; Other; N/A	N/A
CT terminated reason	A detailed reason for why the trial was terminated, if applicable	Free text	e.g., 'Clinical trial terminated due to difficulty enrolling suitable candidates within the study period'	N/A
CT description	Concise description of CT, exactly as presented from the CT source. (i.e., the brief study description lifted from CT.gov)	Free text	e.g., 'This study compared intramuscular carbetocin [Pabal], syntocinon [oxytocin] and syntometrine [oxytocin/ ergometrine] for the third stage of labour following vaginal birth (IMox). Other studies have shown that Carbetocin is slightly better at preventing bleeding after birth when compared to Syntometrine, that it has fewer side effects than Syntometrine, and that it may be just as good as Syntocinon at preventing PPH. No studies have directly compared all three medicines or compared their overall cost.'	Copy the brief description (not the detailed one) exactly as is written from the source. Brief descriptions may be very brief or longer/more descriptive.

Data field	Definition	Data input type	Data example	Additional guidance notes
Clinical trial entry				
CT start date	CT start date as per CT database, written as dd/mm/yyyy	Free text	e.g., 21/03/2020	N/A
CT start type	Whether the start date is the actual or planned start date	Drop-down (list)	e.g., Actual; Planned	N/A
CT end date	CT end date as per CT database, written as dd/mm/yyyy	Free text	e.g., 21/03/2021	Use the "Actual Study Completion Date"
CT end date type	Whether the end date is the actual or planned end date	Drop-down (list)	e.g., Actual; Planned	N/A
CT location(s)	CT location(s) as per CT database	Free text	France; Germany	If unknown, leave blank.
CT enrolment	Actual or planned (whichever is most applicable) number of participants to be enrolled in the study	Numeric	e.g., 250	If unknown, leave blank.
CT results status	Whether CT results have been published (any format).	Drop-down (list)	e.g., Available; Not available	N/A
CT results type	If CT has results, the nature of publication	Drop-down (list)	e.g., Press release; Conference abstract presentation; Clinical trial registry; Preprint article; Peer reviewed article; Other	N/A
CT results source	Link to published source	Free text	e.g., https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(17)30173-6/fulltext	Often not listed on CT entries. Searching CT titles can return relevant papers for trials that have completed (time permitting).
CT sponsor(s)	CT sponsor(s) as per CT database	Free text	e.g., University of Liverpool	N/A
CT collaborators	CT collaborators as per CT database	Free text	e.g., Fogarty International Center of the National Institute of Health	N/A

ANNEXE 2

INCLUDED MEDICINES BY CONDITION, PRODUCT & STATUS[66]

FOETAL DISTRESS

DRUGS

Atosiban – Foetal distress – (Drug; Inactive)
Dydrogesterone – Foetal distress – (Drug; Inactive)
Fenoterol – Foetal distress – (Drug; Inactive)
Glyceryl trinitrate – Foetal distress – (Drug; Inactive)
Hexoprenaline – Foetal distress – (Drug; Inactive)
Magnesium sulphate – Foetal distress – (Drug; Inactive)
Nifedipine – Foetal distress – (Drug; Inactive)
Salbutamol – Foetal distress – (Drug; Inactive)
Sildenafil citrate – Foetal distress – (Drug; Active)
Terbutaline – Foetal distress – (Drug; Inactive)

BIOLOGICS

Haemoglobin-vesicles (nanoparticle delivery) – Foetal distress – (Biologic; Inactive)

POSTPARTUM HAEMORRHAGE (PPH)

DRUGS

Carbetocin – (Drug; Active)
Carbetocin – heat stable (HSC) – (Drug; Active)
Carboprost – (Drug; Active)
Desmopressin – (Drug; Active)
Dinoprost – (Drug; Inactive)
Dinoprostone – (Drug; Inactive)
Dofetilide (nanoparticle delivery) – (Drug; Inactive)
Ergometrine/methylergometrine – (Drug; Active)
Ethamsylate – (Drug; Active)
Melatonin – PPH – (Drug; Active)
Misoprostol – (Drug; Active)
Oxytocin – (Drug; Active)
Oxytocin – heat stable/inhaled – (Drug; Active)
Oxytocin – heat stable/orally disintegrating – (Drug; Inactive)
Oxytocin (Uniject injection device) – (Drug; Inactive)
Oxytocin/ergometrine – fixed dose combination – (Drug; Active)
Phorbol-12,13-dibutyrate – (Drug; Inactive)
Propranolol – (Drug; Active)
Sulprostone – (Drug; Active)
Tranexamic acid – (Drug; Active)
Vasopressin – (Drug; Active)
VU590 Dihydrochloride – (Drug; Inactive)

BIOLOGICS

Eptacog alfa – (Biologic; Active)
Fibrinogen concentrate – (Biologic; Active)
Fresh frozen plasma (FFP) (incl cryoprecipitate) – (Biologic; Active)
Prothrombin complex concentrate (PCC) – (Biologic; Active)
Recombinant von Willebrand factor – (Biologic; Active)

DIETARY SUPPLEMENTS

Herb – Achillea millefolium extract – (Dietary supplement; Active)
Herb – Capsella bursa pastoris – (Dietary supplement; Inactive)
Herb – Motherwort – (Dietary supplement; Inactive)
Herb – Nigella sativa & Anethum graveolens extract – (Dietary supplement; Active)
Herb – Phoenix dactylifera fruit – (Dietary supplement; Active)
Herb – Plantago extract – (Dietary supplement; Active)
Herb – Portulaca oleracea extract – (Dietary supplement; Active)
Herb – Shenghua decoction – (Dietary supplement; Inactive)
Herb – Urtica dioica extract – (Dietary supplement; Active)
Polyphenol – Dill extract – (Dietary supplement; Inactive)
Polyphenol – Grape seed extract – PPH – (Dietary supplement; Active)
Vitamin – Vitamin K – (Dietary supplement; Inactive)

66
Candidate status – active vs inactive – reflects that at the time of writing (June 2021)

INTRAUTERINE GROWTH RESTRICTION (IUGR)

DRUGS

17-alpha-hydroxyprogesterone caproate – IUGR – (Drug; Active)
Allopurinol – (Drug; Inactive)
Allylestrenol – IUGR – (Drug; Inactive)
Amino acid – N-acetylcysteine – IUGR – (Drug; Inactive)
Aspirin – IUGR – (Drug; Active)
Celecoxib – IUGR – (Drug; Inactive)
Chloroquine/Hydroxychloroquine – IUGR – (Drug; Active)
CLR/RAMP agonists – IUGR – (Drug; Inactive)
Dalteparin – IUGR – (Drug; Active)
Enoxaparin – IUGR – (Drug; Active)
Glyceryl trinitrate – IUGR – (Drug; Active)
GYY4137- IUGR – (Drug; Active)
Levothyroxine – IUGR – (Drug; Inactive)
Magnesium sulphate – IUGR – (Drug; Active)
Melatonin – IUGR – (Drug; Active)
Metformin – IUGR – (Drug; Active)
MitoQ (nanoparticle delivery) – (Drug; Active)
MZe786 – IUGR – (Drug; Active)
Nicotine – (Drug; Active)
Ouabain – IUGR – (Drug; Active)
Pentaerithrityl tetranitrate – IUGR – (Drug; Active)
Pentoxifylline – (Drug; Active)
Pravastatin – IUGR – (Drug; Active)
Ropivacaine – IUGR – (Drug; Inactive)
SE175 – nanoparticle delivery – (Drug; Inactive)
Sildenafil citrate – IUGR – (Drug; Active)
Sodium hydrosulfide – IUGR – (Drug; Inactive)
Tadalafil – IUGR – (Drug; Active)
Tempol – IUGR – (Drug; Inactive)
Tinzaparin – (Drug; Inactive)

BIOLOGICS

Ad-VEGF (viral vector delivery) – IUGR – (Biologic; Active)
AGT-targeting siRNA – IUGR – (Biologic; Active)
Antithrombin – (Biologic; Active)
CD28 superagonists – (Biologic; Inactive)
Epidermal growth factor – (Biologic; Inactive)
Functional mitochondria therapy – (Biologic; Active)
Haemoglobin vesicle (nanoparticle delivery) – IUGR – (Biologic; Inactive)
Insulin-like growth factor-1 – (Biologic; Inactive)
Insulin-like growth factor-1 (nanoparticle delivery) – (Biologic; Active)
Insulin-like growth factor-1 (viral vector delivery) – (Biologic; Inactive)
Insulin-like growth factor-2 (nanoparticle delivery) – (Biologic; Inactive)
Insulin-like growth factor-2 (viral vector delivery) – (Biologic; Inactive)
Micro-RNA inhibitors – (Biologic; Inactive)
VEGF-121 – IUGR – (Biologic; Active)

DIETARY SUPPLEMENTS

Amino acid – Creatine (Dietary supplement; Active)
Amino acid – L-arginine – IUGR – (Dietary supplement; Active)
Amino acid – Taurine – (Dietary supplement; Active)
Herb – Abeliophyllum distichum Nakai leaf extract – IUGR – (Dietary supplement; Active)
Herb – Ginkgo biloba extract – IUGR – (Dietary supplement; Inactive)
Herb – Huo Xue Bu Qi Fang – (Dietary supplement; Inactive)
Herb – JLFC01 – (Dietary supplement; Inactive)
Herb – Toki-shakuyaku-san – IUGR – (Dietary supplement; Inactive)
Lycopene – IUGR – (Dietary supplement; Active)
Mineral – Iron – IUGR – (Dietary supplement; Active)
Mineral – Zinc – IUGR – (Dietary supplement; Inactive)
Omega-3 fatty acids – IUGR – (Dietary supplement; Active)
Polyphenol – Punica granatum extract (Punicalagin) – IUGR – (Dietary supplement; Active)
Vitamin – Vitamin B3 – IUGR – (Dietary supplement; Active)
Vitamin – Vitamin B9 – IUGR – (Dietary supplement; Inactive)
Vitamin – Vitamin C – IUGR – (Dietary supplement; Active)
Vitamin – Vitamin D – IUGR – (Dietary supplement; Active)
Vitamin – Vitamin E – IUGR – (Dietary supplement; Active)
Vitamin/Mineral – UNIMMAP micronutrient tablet – IUGR – (Dietary supplement; Active)

PREECLAMPSIA/ECLAMPSIA (PE/E)

DRUGS

17-alpha-hydroxyprogesterone caproate – PE/E – (Drug; Active)
Amlodipine – (Drug; Active)
AP39 – (Drug; Active)
Aspirin – PE/E – (Drug; Active)
Atenolol – PE/E – (Drug; Inactive)
Azathioprine – (Drug; Inactive)
Benazepril – (Drug; Inactive)
BMS582949 – (Drug; Inactive)
Captopril – (Drug; Inactive)
Carveol – (Drug; Active)
Celastrol – (Drug; Inactive)
Celecoxib – PE/E – (Drug; Inactive)
Chloroquine/Hydroxychloroquine – PE/E – (Drug; Active)
Cibinetide – (Drug; Active)
Clonidine – (Drug; Inactive)
CLR/RAMP agonists – PE/E – (Drug; Inactive)
Cyclosporin A – (Drug; Active)
Dalteparin – PE/E – (Drug; Inactive)
Dasatinib – (Drug; Inactive)
Diltiazem – (Drug; Active)
Doramapimod – (Drug; Inactive)
Dydrogesterone – PE/E – (Drug; Active)
Enalapril – (Drug; Active)
Enoxaparin – PE/E – (Drug; Active)
Esomeprazole – PE/E – (Drug; Active)
Estradiol – (Drug; Active)
Furosemide – (Drug; Active)
Gefitinib – (Drug; Active)
Glyceryl trinitrate – PE/E – (Drug; Inactive)
GYY4137 – PE/E – (Drug; Active)
HTHQ – (Drug; Active)
Hydralazine – (Drug; Inactive)
Hydrochlorothiazide – (Drug; Active)
Hydrogen rich saline – (Drug; Inactive)
Iloprost – (Drug; Inactive)
Isosorbide dinitrate – PE/E – (Drug; Inactive)
Isosorbide mononitrate – (Drug; Active)
Ketanserin – (Drug; Inactive)
Labetalol – (Drug; Active)
Levetiracetam – (Drug; Active)
Liraglutide – (Drug; Active)
Losartan – (Drug; Inactive)
Lovastatin – PE/E – (Drug; Inactive)
Magnesium sulphate – PE/E – (Drug; Active)
Melatonin – PE/E – (Drug; Active)
Menadione – (Drug; Inactive)
Metformin – PE/E – (Drug; Active)
Methyldopa – (Drug; Active)
Methylprednisolone – (Drug; Inactive)
Metoprolol – (Drug; Active)
Moxonidine – (Drug; Inactive)
Mycophenolate mofetil – (Drug; Inactive)
MZe786 – PE/E – (Drug; Active)
Nadroparin – (Drug; Inactive)
Nicardipine – PE/E – (Drug; Inactive)
Nicorandil – PE/E – (Drug; Active)
Nifedipine – PE/E – (Drug; Active)
Nimodipine – (Drug; Inactive)
Ouabain – PE/E – (Drug; Inactive)
Ozagrel – (Drug; Inactive)
Pentaerithrityl tetranitrate – PE/E – (Drug; Inactive)
Phenytoin – (Drug; Inactive)
Pirmagrel – (Drug; Inactive)
PMZ 2123 – (Drug; Inactive)
Pravastatin – PE/E – (Drug; Active)
Progesterone, natural (oral) – PE/E – (Drug; Inactive)
Research programme – GPCR-AAB binding aptamers – (Drug; Inactive)
Research programme – Gynaecological disorder therapeutics – (Drug; Active)
Ropivacaine – PE/E – (Drug; Inactive)
Rosuvastatin – (Drug; Active)
Saireito – (Drug; Inactive)
Salsalate – (Drug; Active)
SB203580 – (Drug; Active)
Sildenafil citrate – PE/E – (Drug; Active)
Simvastatin – PE/E – (Drug; Active)
S-Nitrosoglutathione – PE/E – (Drug; Inactive)
Sodium hydrosulfide – PE/E – (Drug; Inactive)
Sodium nitroprusside – (Drug; Active)

PREECLAMPSIA/ECLAMPSIA (PE/E) (continued)

Sofalcone – (Drug; Inactive)
Sulfasalazine – PE/E – (Drug; Active)
Tadalafil – PE/E – (Drug; Active)
Tempol – PE/E – (Drug; Inactive)
Tetramethylpyrazine – (Drug; Active)
Toki-shakuyaku-san – PE/E – (Drug; Active)
Trehalose – (Drug; Active)
TRV027 – (Drug; Active)
Ulinastatin – PE/E – (Drug; Active)
Urapidil – (Drug; Inactive)
Vardenafil – (Drug; Inactive)
YC 1 – (Drug; Inactive)

BIOLOGICS

Ad-VEGF (viral vector delivery) – PE/E – (Biologic; Inactive)
AGT-targeting siRNA – PE/E – (Biologic; Active)
AMAG 423 – (Biologic; Active)
Antithrombin alfa – (Biologic; Inactive)
Antithrombin gamma – (Biologic; Active)
Antithrombin III – (Biologic; Inactive)
Apolipoprotein A-I – (Biologic; Inactive)
Conestat alfa – (Biologic; Active)
Drotrecogin alfa – (Biologic; Inactive)
Eculizumab – (Biologic; Active)
Emiplacel – (Biologic; Inactive)
Etanercept – PE/E – (Biologic; Active)
Gelsolin – (Biologic; Inactive)
Haemoglobin-vesicles (nanoparticle delivery) – PE/E – (Biologic; Inactive)
Placental growth factor – (Biologic; Active)
Probiotic Lactobacilli – PE/E – (Biologic; Active)
Regulatory T cells – (Biologic; Inactive)
RMC 035 – (Biologic; Active)
Serelaxin – (Biologic; Inactive)
sFlt-1-targeting siRNA – (Biologic; Active)
sFlt-1-targeting siRNA (nanoparticle delivery) – (Biologic; Active)
SynB1-ELP-p50i (polypeptide delivery) – (Biologic; Active)
VEGF-121 – PE/E – (Biologic; Inactive)
VEGF-B (polypeptide delivery) – (Biologic; Active)
VG 1177 – (Biologic; Inactive)

DIETARY SUPPLEMENTS

Amino Acid – L-arginine – PE/E – (Dietary supplement; Active)
Amino Acid – L-citrulline – PE/E – (Dietary supplement; Active)
Amino Acid – L-ergothioneine – (Dietary supplement; Active)
Coenzyme Q10 – PE/E – (Dietary supplement; Active)
Ferulic acid – (Dietary supplement; Active)
Herb – Boiogito – (Dietary supplement; Inactive)
Herb – Euterpe oleracea – (Dietary supplement; Active)
Herb – Garlic extract – (Dietary supplement; Inactive)
Herb – Thymus schimperi – (Dietary supplement; Active)
Lycopene – PE/E – (Dietary supplement; Inactive)
Mineral – Calcium – PE/E – (Dietary supplement; Active)
Mineral – Magnesium – PE/E – (Dietary supplement; Active)
Mineral – Selenium – PE/E – (Dietary supplement; Inactive)
Mineral – Zinc – PE/E – (Dietary supplement; Active)
MitoQ – (Dietary supplement; Active)
Omega-3 fatty acids – PE/E – (Dietary supplement; Active)
Polyphenol – Camelia sinensis (Epigallocatechin gallate) – (Dietary supplement; Inactive)
Polyphenol – Curcuma longa (Curcumin) – (Dietary supplement; Active)
Polyphenol – Grape seed extract – PE/E – (Dietary supplement; Active)
Polyphenol – Mangiferin – (Dietary supplement; Active)
Polyphenol – Moringa oleifera – (Dietary supplement; Active)
Polyphenol – Punica granatum extract (Punicalagin) – PE/E – (Dietary supplement; Active)
Polyphenol – Quercetin – (Dietary supplement; Active)
Polyphenol – Resveratrol – PE/E – (Dietary supplement; Active)
Polyphenol – Salvia miltiorrhiza (Salvianolic acid A) – (Dietary supplement; Inactive)
Polyphenol – Scutellaria baicalensis root extract (Baicalin) – (Dietary supplement; Active)
Polyphenol – Silybum marianum (Silibinin) – PE/E – (Dietary supplement; Active)
Polyphenol – Uncaria rhynchophylla extract – (Dietary supplement; Active)
Polyphenol – Vitexin – (Dietary supplement; Active)
Polyphenol – Vitis labrusca/vinifera extract – (Dietary supplement; Active)
Sulforaphane – (Dietary supplement; Active)
Vitamin – Vitamin A – PE/E – (Dietary supplement; Active)
Vitamin – Vitamin B12 – PE/E – (Dietary supplement; Inactive)
Vitamin – Vitamin B3 – PE/E – (Dietary supplement; Active)
Vitamin – Vitamin B9 – PE/E – (Dietary supplement; Active)
Vitamin – Vitamin C – PE/E – (Dietary supplement; Active)
Vitamin – Vitamin D – PE/E – (Dietary supplement; Active)
Vitamin – Vitamin E – PE/E – (Dietary supplement; Active)

PRETERM LABOUR/BIRTH (PTL/PTB)

DRUGS

(+)-Naloxone – (Drug; Active)
(+)-Naltrexone – (Drug; Active)
[D-Arg8]-inotocin – (Drug; Inactive)
1,10-Phenanthroline – (Drug; Inactive)
15d-PGJ2 – (Drug; Inactive)
17-alpha-hydroxyprogesterone caproate (oral) – PTL/PTB – (Drug; Active)
17-alpha-hydroxyprogesterone caproate (injectable) – PTL/PTB – (Drug; Active)
18b-glycyrrhetinic acid – (Drug; Active)
4APDPMe – (Drug; Active)
4NO2PDPMe – (Drug; Active)
AG126 – (Drug; Inactive)
AG1288 – (Drug; Inactive)
AH 13205 – (Drug; Inactive)
Allylestrenol – PTL/PTB – (Drug; Active)
Alpha-bisabolol – (Drug; Inactive)
Amiloride – (Drug; Inactive)
Amino Acid – N-acetylcysteine – PTL/PTB – (Drug; Active)
Amino Acid – N-acetylcysteine (nanoparticle delivery) – (Drug; Inactive)
Aminophylline – (Drug; Active)
AS603831 – (Drug; Inactive)
AS604872 – (Drug; Inactive)
Aspirin – PTL/PTB – (Drug; Active)
Atosiban – PTL/PTB – (Drug; Active)
Azapeptide analogues – (Drug; Active)
Barusiban – (Drug; Inactive)
Bedoradrine – (Drug; Inactive)
Benzbromarone – (Drug; Active)
Betamethasone – PTL/PTB – (Drug; Active)
BRL 37344 – (Drug; Inactive)
Butaprost – (Drug; Active)
Carvacrol – (Drug; Active)
Celecoxib – PTL/PTB – (Drug; Inactive)
Chloroquine/Hydroxychloroquine – PTL/PTB – (Drug; Active)
Citral – (Drug; Active)
CLR/RAMP agonists – PTL/PTB – (Drug; Inactive)
CyPPA – (Drug; Inactive)
Dexamethasone – PTL/PTB – (Drug; Active)
Dydrogesterone – PTL/PTB – (Drug; Active)
Ebopiprant – (Drug; Active)
Esomeprazole – PTL/PTB – (Drug; Inactive)
Fenoterol – PTL/PTB – (Drug; Active)
Glyceryl trinitrate – PTL/PTB – (Drug; Active)
GW405212X – (Drug; Inactive)
GYY4137 – PTL/PTB – (Drug; Inactive)
HC067047 – (Drug; Inactive)
Hexoprenaline – PTL/PTB – (Drug; Inactive)
Histone deacetylase inhibitors (nanosuspension) – (Drug; Active)
Hydrazone sulfanilide oxytocin antagonists – (Drug; Inactive)
Hydrogen peroxide – PTL/PTB – (Drug; Inactive)
IMD-0560 – (Drug; Inactive)
Indomethacin – (Drug; Active)
Indomethacin (nanoparticle delivery) – (Drug; Inactive)
Isosorbide dinitrate – PTL/PTB – (Drug; Inactive)
Isoxsuprine – (Drug; Active)
Isradipine – (Drug; Inactive)
Ketoprofen – (Drug; Inactive)
KUR-1247 – (Drug; Inactive)
L 368899 – (Drug; Inactive)
Lansoprazole – (Drug; Active)
LDD175 – (Drug; Inactive)
Levosimendan – (Drug; Inactive)
Levothyroxine – PTL/PTB – (Drug; Inactive)
Magnesium sulphate – PTL/PTB – (Drug; Active)
Medroxyprogesterone acetate – PTL/PTB – (Drug; Inactive)
Melatonin – PTL/PTB – (Drug; Active)
Meloxicam – (Drug; Inactive)
Meluadrine tartrate – (Drug; Inactive)
Metoclopramide – (Drug; Active)
MONNA – (Drug; Active)
Montelukast – (Drug; Inactive)
Nebivolol – (Drug; Active)
Nicardipine – PTL/PTB – (Drug; Inactive)
Nicorandil – PTL/PTB – (Drug; Active)
Nifedipine – PTL/PTB – (Drug; Active)
Nifedipine (nanoparticle delivery) – PTL/PTB – (Drug; Inactive)
Nimesulide – (Drug; Inactive)
Nolasiban – PTL/PTB – (Drug; Inactive)
NS-398 – (Drug; Inactive)

PRETERM LABOUR/BIRTH (PTL/PTB) (continued)

Omeprazole – (Drug; Inactive)
ONO 8815Ly – (Drug; Inactive)
Orciprenaline – (Drug; Inactive)
OXznl – (Drug; Inactive)
Paeoniflorin – (Drug; Inactive)
PAMAM dendrimer – antibacterial nanoparticles – (Drug; Inactive)
Pantoprazole – (Drug; Inactive)
Parthenolide – (Drug; Inactive)
PDC113.824 – (Drug; Inactive)
Pen-NBD (cell-penetrating peptide delivery) – (Drug; Inactive)
Pentaerythrityl tetranitrate – PTL/PTB – (Drug; Active)
PGN-1473 – (Drug; Inactive)
PGN-9856 – (Drug; Active)
Pinacidil – (Drug; Inactive)
Pravastatin – PTL/PTB – (Drug; Active)
Progesterone, natural, micronized (oral) – PTL/PTB – (Drug; Active)
Progesterone, natural, micronized (vaginal/topical) – PTL/PTB – (Drug; Active)
Progesterone, natural, nanosuspension (topical/vaginal) – (Drug; Active)
Rabeprazole – (Drug; Inactive)
Relcovaptan – (Drug; Inactive)
Replens gel – (Drug; Active)
Retigabine – (Drug; Inactive)
Retosiban – (Drug; Inactive)
Ritodrine – (Drug; Inactive)
Rofecoxib – (Drug; Inactive)
Rolipram – (Drug; Inactive)
Rolipram (nanoparticle delivery) – (Drug; Inactive)
Rytvela – (Drug; Active)
Salbutamol – PTL/PTB – (Drug; Inactive)
Salbutamol (nanoparticle delivery) – (Drug; Inactive)
SAR-150640 – (Drug; Inactive)
SB 202190 – (Drug; Inactive)
SB 239063 – (Drug; Inactive)
Sc514 – (Drug; Inactive)
SCH-772984 – (Drug; Inactive)
Sildenafil citrate – PTL/PTB – (Drug; Active)
Simvastatin – PTL/PTB – (Drug; Active)
Sirolimus – (Drug; Inactive)
SKF-86002 – (Drug; Inactive)
S-Nitrosocysteine – (Drug; Inactive)
S-Nitrosoglutathione – PTL/PTB – (Drug; Active)
Sodium hydrosulfide – PTL/PTB – (Drug; Inactive)
SSR-126768A – (Drug; Inactive)
Sulfasalazine – PTL/PTB – (Drug; Inactive)
Sulindac – (Drug; Inactive)
Super-repressor (SR) IκBα (exosome delivery) – (Drug; Active)
Terbutaline – PTL/PTB – (Drug; Active)
THG113.31 – (Drug; Inactive)
TLR4A (synthetic) – (Drug; Inactive)
TPCA-1 – (Drug; Inactive)
TT 235 – (Drug; Inactive)
U-0126 – (Drug; Inactive)
Y-27632 – (Drug; Inactive)
ZD-7288 – (Drug; Inactive)

BIOLOGICS

Anakinra – (Biologic; Inactive)
Anti-TLR4 monoclonal antibodies – (Biologic; Inactive)
Botulinum toxin A – (Biologic; Inactive)
Etanercept – PTL/PTB – (Biologic; Inactive)
Exendin-4 – (Biologic; Active)
Exosome-based protein therapeutic – (Biologic; Active)
Human chorionic gonadotropin – (Biologic; Inactive)
Lactoferrin – (Biologic; Active)
Leptin – (Biologic; Inactive)
Microbiome therapeutics – (Biologic; Active)
Probiotic Lactobacilli – PTL/PTB – (Biologic; Active)
Surfactant Protein A – (Biologic; Inactive)
Tocilizumab – (Biologic; Inactive)
Ulinastatin – PTL/PTB – (Biologic; Inactive)

ANNEXE 2
INCLUDED MEDICINES BY CONDITION, PRODUCT & STATUS

DIETARY SUPPLEMENTS

Alpha-lipoic acid – (Dietary supplement; Active)
Amino Acid – L-arginine – PTL/PTB – (Dietary supplement; Inactive)
Herb – Abeliophyllum distichum Nakai leaf extract – PTL/PTB – (Dietary supplement; Active)
Herb – Ananas comosus, ethyl acetate fraction – (Dietary supplement; Inactive)
Herb – Astragali radix extract – (Dietary supplement; Inactive)
Herb – Bryophyllum pinnatum extract – (Dietary supplement; Active)
Herb – Cucurbita moschata extract – (Dietary supplement; Active)
Herb – Curcuma aeruginosa rhizome extract – (Dietary supplement; Inactive)
Herb – Pimpinella anisum extract – (Dietary supplement; Active)
Herb – Zishen Yutai Pill – PTL/PTB – (Dietary supplement; Inactive)
Lycopene – PTL/PTB – (Dietary supplement; Active)
Mineral – Calcium – PTL/PTB – (Dietary supplement; Active)
Mineral – Iodine – (Dietary supplement; Inactive)
Mineral – Iron – PTL/PTB – (Dietary supplement; Active)
Mineral – Magnesium – PTL/PTB – (Dietary supplement; Active)
Mineral – Selenium – PTL/PTB – (Dietary supplement; Active)
Mineral – Zinc – PTL/PTB – (Dietary supplement; Active)
Omega-3 fatty acids – PTL/PTB – (Dietary supplement; Active)
Polyphenol – Galetin 3,6-dimethyl ether – (Dietary supplement; Inactive)
Polyphenol – Gallic acid – (Dietary supplement; Active)
Polyphenol – Honokiol – (Dietary supplement; Inactive)
Polyphenol – Nobiletin – (Dietary supplement; Inactive)
Polyphenol – Resveratrol – PTL/PTB – (Dietary supplement; Inactive)
Polyphenol – Scutellaria baicalensis root extract (Oroxylin A) – (Dietary supplement; Inactive)
Polyphenol – Silybum marianum (Silibinin) – PTL/PTB – (Dietary supplement; Inactive)
Polyphenol – Tannic acid – (Dietary supplement; Inactive)
Vitamin – Vitamin A – PTL/PTB – (Dietary supplement; Inactive)
Vitamin – Vitamin B12 – PTL/PTB – (Dietary supplement; Inactive)
Vitamin – Vitamin B9 – PTL/PTB – (Dietary supplement; Active)
Vitamin – Vitamin C – PTL/PTB – (Dietary supplement; Inactive)
Vitamin – Vitamin D – PTL/PTB – (Dietary supplement; Active)
Vitamin – Vitamin E – PTL/PTB – (Dietary supplement; Inactive)

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