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PregOMICS - leveraging systems biology and bioinformatics for drug repurposing in maternal-child health

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Abstract

Problem—Obstetric diseases remain underserved and understudied. Drug repurposing – utilization of a drug whose use is accepted in one condition for a different condition – could represent a rapid and low-cost way to identify new therapies that are known to be safe. In diseases of pregnancy, the known safety profile is a strong additional incentive.

Method of Study—Narrative review

Results—We describe the techniques and steps used in the use of ‘omics data for drug repurposing. We illustrate these techniques using case studies of published drug repurposing projects. We provide a set of available databases with low barriers to entry which investigators can use to perform their own projects.

Conclusions—Using ‘omics techniques provides the promise of unbiased screening all drug targets or all patients using particular drugs to find which are likely to alter disease risk or progression. However, we caution that reproducibility across the underlying studies, and thus the drugs suggested for repurposing, can be poor. We suggest that improved nosology, for example correlating patient clinical conditions with placental pathology, could yield more robust associations. We conclude that ‘omics driven drug repurposing represents a potential fruitful path to discover new, safe treatments of obstetric diseases.

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Conflicts of interest

The authors state no conflict of interest.

Graphical Abstract

Keywords

GWAS; omics; drug repurposing; obstetrics; diseases of pregnancy

Introduction

Obstetrical disease incidence is increasing and outcomes are worsening. The most dramatic evidence is the increasing maternal mortality rate in the United States¹. Improvements in late fetal and neonatal mortality rates have stagnated^{1–3}. While much of this can be attributed to systemic problems of inequality in access to care, there are generous areas for improvement in the efficacy of that care. Ideally, more effective care would reduce the negative effects of low-resource care, both in the United States and globally. Limiting our view to perinatal events may also mislead as to the effectiveness of treatment because it may miss pregnancy complications that occur in both mothers and offspring long after delivery. For example, therapies for gestational diabetes (GDM), including diet, insulin, and oral hypoglycemics, are effective at controlling blood sugar and reducing rates of large for gestational age (LGA) infants⁴. However, treatment must be continued post-partum to ameliorate the elevated risk of type 2 diabetes in affected mothers, and these therapies do not decrease BMI and fasting glucose in children 8–10 years after birth⁵. The increasing age of the pregnant population brings additional challenges of managing pre-existing diseases in pregnancy with fewer medications known to be safe in this population given the risk of teratogenesis.

These findings underline the challenges in diseases of pregnancy. Interventions must work on altered maternal physiology, fetal physiology, and the biology of the placenta⁶. In the face of these challenges, it is unfortunate that drug development and clinical trials infrequently address gestation. Fewer than 0.5% of registered clinical trials study pharmacologic therapy in pregnancy⁷. The number of trials studying specific pregnancy complications such as preterm birth or pre-eclampsia is 40–50 fold lower than the number of trials studying other diseases with equivalent incidences, such as breast or lung cancer⁷. The very real clinical, safety, and regulatory challenges of working in diseases of pregnancy partially explain the lack of commercially sponsored clinical trials, however given the associated insufficiency of government and foundation sponsored research, this might

become a “vulnerable population” that is so protected, research is hardly ever conducted⁸. These data support the impression that all diseases of pregnancy are orphan diseases⁷.

Drug repurposing

Drug repurposing, or repositioning, is the utilization of a drug whose use is accepted in one condition in a different condition⁹. This strategy seems particularly well-suited to diseases of pregnancy. There are three broad categories whereby a drug is repurposed, representing a spectrum of complexity (Figure 1).

The first of these, redeployment, occurs when a drug with a defined indication is redeployed for use in the same condition(s) but in a different setting, such as pregnancy. This may appear trivial, and some would not consider this repurposing per se, but we mention it to highlight the new biology which may be revealed. For example, concerns for increased risk of suicide when starting antidepressants only emerged after a study of the adolescent population¹⁰. Previously effective treatment regimens can also become ineffective, for example in the increased risk of ulcerative colitis flares in pregnancy and the post-partum period¹¹.

The second form of repurposing, indication expansion, is when a drug that is well established in treating one condition is used to treat a related disease. This may also not be considered repurposing, but we include it because it underlines the mechanistic and clinical understanding required for successful repurposing. The cross-functionality of TNF inhibitors for inflammatory bowel disease, psoriasis, and rheumatoid arthritis reflect the autoimmune nature of these disparate illnesses¹². Conversely, hypertension in pregnancy and essential hypertension have disparate pathogeneses but shared clinical manifestations¹³.

The third and most radical form of repurposing is when a drug is used far outside its usual functional indication. The most dramatic example in the obstetric realm is the use of acetylsalicylic acid (Aspirin) for prevention of pre-eclampsia¹⁴. This example is impressive because the attempt at repurposing was made without knowing the mechanism of pre-eclampsia.

The examples above illustrate two clear advantages of drug repurposing. The first is that the agent of interest already exists as a drug; thus, the problems of chemical synthesis, pharmacokinetics, pharmacodynamics, and drug-drug interactions have been (mostly) worked out. The second is the presumption of efficacy in humans for at least some diseases. We would argue that even the 3rd class of repurposing carries the presumption that the drug under investigation will have some effect, even if it is not on the disease of interest. In this way, repurposing is suggested to bridge the so-called “valley of death” in drug development (Figure 2). In this valley, promising drug targets or candidate molecules languish outside the clinic due to the gap in funding and expertise.

Pregnancy adds a second (and perhaps more daunting) valley: the special safety concerns of pregnancy, specifically preterm birth, pregnancy loss, and teratogenesis. Teratogenesis is particularly difficult to predict and can have devastating long-term consequences that may not be apparent for years. For example, women with *in utero* exposure to diethylstilbestrol

did not start manifesting vaginal clear cell carcinoma until their 20's¹⁵. This second valley makes drug repurposing more attractive for the small group of molecules that are considered safe in the pregnant population.

Incentives for drug repurposing

Few drugs have shown safety in pregnancy after rigorous clinical trials. The evidence is more commonly extended from post-marketing clinical experience without increased reports of adverse events¹⁶. This means that most drugs considered safe in pregnancy are off-patent, which makes them attractive from a global health perspective. The U.S. Food and Drug Administration (FDA) meanwhile grants 3 year periods of exclusivity for a new indication of an old molecule based on new clinical studies¹⁷.

Using 'omics studies for drug repurposing

The first step in a drug repurposing study is to identify candidate drugs. Multiple databases of molecules with known or purported biologic activity are available. However, the need for safety suggests that the drugs under consideration should be confined to those known, or thought to be, safe in pregnancy. This corresponds to the historical pregnancy category A and B drugs used by the U.S. Recently, the FDA has replaced them with statements about drug safety¹⁸. For our studies, we used the Australian Therapeutic Goods Agency (TGA) classification, in which category A and B1 roughly correspond to the categories of interest. The TGA database is searchable and provides information in an easily downloadable table <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>¹⁹. Some drugs that are widely used in pregnancy, for example selective serotonin reuptake inhibitors (SSRIs) for depression, are category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans). Investigators may nonetheless choose to include category C drugs due to their broad use. For severe diseases, the risk from medications may be balanced by the disease that they treat. In either case, investigators should seek evidence to inform the risk:benefit balance.

'Omics strategies

Target driven strategies

As the name implies, the key step in target driven strategies is identification of the protein/ gene targets of candidate drugs. The nature of this step relies on the 'omics technique being used. Using the central dogma, we infer that a drug that targets a specific protein, for example by inhibiting its activity, also "targets" the gene and transcript encoding the protein. Since these proteins are well characterized, databases such as the Drug Bank (<https://www.drugbank.ca/>) or the psychoactive drug screening program (PDSP, <https://pdsp.unc.edu/databases/pdsp.php>) are helpful resources for identifying drug-target protein associations^{20,21}. Investigators still need to closely examine such associations. For example, one might choose to further interrogate the reported link between caffeine and the DNA damage detection protein Ataxia Telangiectasia Mutated (ATM). The "pharmacologic action" subset may be more relevant. The inhibitory constant (K_i, or binding affinity) values from PDSP should be interpreted in light of the protein expression in known target tissues, for

example the PDSP G-protein coupled receptor database²². Similar groundwork should be performed for other target based strategies, including metabolomics and some literature-based strategies. Including signal transduction proteins or other downstream mediators can be helpful, but if those mediators are shared across several pathways, the results become difficult to interpret. For example, many signaling pathways act through cyclic AMP, and variants in adenylate cyclase 5 (*ADCY5*) have been associated with GDM. However, because many drugs target signaling pathways that include *ADCY5*, additional information is needed to discern which pathway is activating adenylate cyclase²³.

Most drugs have multiple targets. Even when a drug targets a single receptor, the receptor may be comprised of multiple proteins. The most straightforward approach is to determine whether any target protein has a strong *P*-value for disease association. Signals for multiple genes can be integrated via gene set enrichment analysis (GSEA)²⁴. Non-drug targets can be linked to targets via protein-protein interactions (PPI), again with some loss of specificity²⁵. PPI and gene expression in relevant tissues can be used to prioritize underwhelming hits, which can be further studied for validation²⁶.

An example of a successful target driven strategy is the study of Zhang et al. on Alzheimer Disease (AD)²⁷. The group identified SNPs associated with AD using the GWAS catalog (<https://www.ebi.ac.uk/gwas/>), bypassing the need to develop their own cohort²⁸. Proteins with altered expression in AD were identified by PubMed search, and metabolites were identified using the Human Metabolome Database (HMDB). The authors then linked the genes, proteins, and metabolites. The list of potential target genes and proteins was filtered, limiting it to those that were associated with at least 2 AD-associated metabolites. The list was further winnowed by examining the result of pathogenic mutations in target genes using Online Mendelian Inheritance in Man (OMIM), supplemented by manually examining phenotypes of gene knockout mice. Target genes were then surveyed against the Therapeutic Target Database (TTD) and DrugBank to identify which drugs targeted proteins that were associated with AD. The resulting proteins and drugs were subjected to a ranking assay that used the degree of similarity between target protein's PPI and known AD proteins (*e.g.* presenilin), and similarity of drug target PPI to that of known AD drugs (*e.g.* galantamine, memantine), among others. The top ranked candidate drugs were monoclonal antibodies against 2 proteins expressed on microglia - CD33 and Migration Inhibitory Factor (MIF). Runners up included other drugs targeting microglia. Publication is a measure of success in repurposing, but regulatory approval is the ultimate goal. Despite extensive press relatively few 'omics-based efforts have made it to clinical use. In this case, for example, we were unable to identify trials registered on ClinicalTrials.gov or reported in the literature using antibodies to CD33 or MIF to treat or prevent AD.

Disease driven strategies

In disease driven strategies, patients with a disease are investigated for a history of drug exposure. High-throughput versions of this strategy, which we refer to as *PregOMICS* rely on electronic health records (EHR). When using this strategy, it is important to have an easily identified disease, possibly driven by lab results or international classification of disease (ICD) codes. A definition of drug exposure should be determined. Exposure

definitions could include A) ever mentioned in a patient chart; B) mentioned before or on the date of diagnosis; C) mentioned at least 3 months prior to pregnancy and continued. Depending on how drugs are recorded, multiple synonyms may be required to find mentions of drugs in the EHR. For both disease and drug ascertainment, investigators must balance the amount of information required to designate a patient a case or a control against the risk of over-excluding patients and using a study group that is either too small or unrepresentative of the patient population.

In an example of successful disease-driven strategy outside of pregnancy, Brilliant, *et al.* used EHR and prescription database records to identify an association between age-related macular degeneration (AMD) and L-Dopa exposure. On closer examination, prescription for L-Dopa was associated with later development of AMD, while patients with AMD were frequently prescribed L-Dopa subsequent to diagnosis²⁹. This suggested that L-Dopa could be used to prevent or treat AMD. Subsequently, 4 clinical trials have begun (ClinicalTrials.gov trials NCT02863640, NCT02873351, NCT03023059, and NCT03022318). The results have yet to be reported, but even so, this is rapid progress. EHR-based studies can also be used to validate basic science findings for medical use. Metformin was shown in animal models to decreased cancer proliferation, and an EHR study showed that use was associated with improved cancer mortality, prompting prospective trials³⁰.

The distinction between target and disease-driven strategies is theoretical and should not impair studies which include both arms. For example, in our recent repurposing paper on GDM, we used a target-driven GWAS strategy and a disease driven EHR strategy³¹. For our target driven strategy, we selected drugs and identified targets using the resources mentioned above. We used SNP-disease associations from the Vanderbilt BioVU cohort and gene set analysis for the targets of each drug. In parallel, we used the de-identified EHR to identify drug exposures associated with changes in the glucose tolerance test. Because our structure was relatively straightforward with only 2 arms, we suggested the intersection – antinausea serotonin receptor 3 antagonists (e.g. ondansetron) and calcium channel blocking antihypertensives (nifedipine) as targets for future study (Figure 3, ³¹).

Resources

One advantage of ‘omics data is the vast quantity, much of which has yet to be directly examined by a human mind. Several large data sets and catalogs are publicly available and privately generated data from one modality can be supplemented with public data using a different method (Table). In theory, data derived from multiple modalities should be independent, improving reliability. Drug candidates identified by multiple modes should be more likely to represent true hits. Two caveats should be kept in mind. First, data sets should be validated by their ability to replicate known results. For example, a GWAS for GDM should be able to replicate variants in *TCF7L2*. Second, many data sets are not designed with pregnancy in mind, and so may not report pregnancy-specific conditions or tissues, may not include pregnant women, or may use women who have never been pregnant (or men(!)) as controls in case:control studies.

The GWAS catalog is an excellent starting place since it captures many individual studies²⁸. The UK Biobank is a set of 500,000 individuals in the United Kingdom. GWAS for ~2400 traits from the UK Biobank, including some pregnancy-specific diseases, are publicly available (<https://sites.google.com/broadinstitute.org/ukbbgwasresults/home> ; <http://pheweb.sph.umich.edu:5003/> ; ^{32,33}). Public data sets for PPI, tissue expression, and expression quantitative trait loci (eQTL) can also provide insights into drug function. The Gene-Tissue Expression (GTEx) project (<https://www.gtexportal.org>) is a large collection of tissue specific eQTLs³⁴. This database has been crossed with public large-scale GWAS studies, such as the UK Biobank in a project known as PrediXcan (<http://gene2pheno.org/> ; ³⁵). These results have the added benefit of approximating potential tissue specificity in the absence of transcriptomic data. However, GTEx, and therefore PrediXcan, lacks key gestational tissues including placenta, umbilical cord, fetal and pediatric tissues, and the gravid uterus. Additionally, interpretation is not always straightforward. For example, the strongest reported PrediXcan association for preterm birth is with genetically determined variation in expression of the serotonin type 2A receptor (HTR2A) in the testes. Unfortunately, there is no publicly available EHR dataset, likely owing to privacy concerns. However, the widespread adoption of EHR systems means that hospital-associated investigators will be able to acquire some data. Use of such systems will generally require IRB approval and help composing and executing queries, often at a cost to investigators.

Intregation

An ideal drug repurposing study uses and integrates multiple independent methods. If few methods are used, as in our recent study this can be performed by hand ³¹. Safety information, if available, can be used for further prioritization. Other studies are more complex. A drug repurposing study for rheumatoid arthritis is an example of integration of multiple sources of novel and publicly available data⁹. In this study, a large GWAS meta-analysis was combined with known variants in the GWAS catalog. The associations occurred in 100 regions across the genome which contained 377 genes. Association of SNPs with genes is not always straightforward. The effect of a SNP located in one gene may be due to its linkage with a variant in a second gene. To control for this effect, the authors determined whether protein-altering variants in a gene of interest were in linkage disequilibrium (i.e. co-inherited) with the identified SNPs, and whether the gene of interest was closest to the strongest SNP. Genes were further rated based on their association with primary immunodeficiency, lymphomas and leukemias, autoimmune phenotypes in knockout mice, and enrichment in PubMed publications on rheumatoid arthritis. Further steps included identifying which genes are expressed in lymphocyte subsets implicated in rheumatoid arthritis by histone methylation profiling, checking which proteins were targets of drugs known to treat rheumatoid arthritis or had protein-protein interactions with proteins that did. Further protein-protein interaction linked rheumatoid-arthritis associated proteins to known drug targets. Candidate target genes were rated on whether they showed significant effect or association on each metric, and the targets prioritized by the number of points. The drugs targeting these proteins were suggested for repurposing.

Cold water

In general, the strongest hits in repurposing studies will tend to be drugs that are already known to be useful in the condition of interest. In our recent study of GDM, for example, the strongest EHR associations for blood glucose in a glucose tolerance test were 3 drugs currently used to treat GDM³¹. Conversely, if known targets of drugs commonly applied to a particular condition give a weak or nonsignificant association, it could raise concerns that the study is unreliable.

The largest challenge for PregOMICS is reproducibility in ‘omics studies of pregnancy complications. In a landmark study by Eidem et al., there was minimal reproducibility of gene expression changes within and between causes of preterm birth³⁶. Similarly, some GWAS have generated significant results, but these findings were not replicated between studies^{37–39}. To some extent, this reflects the under-resourcing of diseases of pregnancy, as noted in the introduction. However, we believe that it occurs in large part due to poor nosology. The most pressing diseases of pregnancy and birth – preterm birth, small for gestational age (SGA / fetal growth restriction [FGR]), maternal hemorrhage, premature rupture of membranes – are heterogeneous. They may better be thought of as syndromes or constellations of clinical features that can result from a myriad of distinct pathogenetic mechanisms. For example, the pathologic findings in SGA infants are divided into maternal vascular malperfusion (pre-eclampsia, hypertension, smoking), alloimmune (chronic villitis), and fetal (genetic anomalies, constitutional, etc.) causes⁴⁰. GWAS of SGA/FGR has not been reported, and if performed would be unlikely to produce useful information unless including very large sample sizes. Even if signals were identified, they may not replicate in another cohort if it had a different mixture of underlying diseases. Refined diagnosis of obstetric disease is beyond the scope of this paper, however we suggest that more refined classification considering disease etiology may yield more accurate results. Sufficiently large ‘omics studies could also separate patients based on their underlying methylation or expression signature, as has been done in some cancers^{41,42}.

The future

We believe ‘omics based drug repurposing in diseases of pregnancy could have dramatic impact. In part, this reflects the poor prospects of other avenues for new therapies in pregnancy, however it is also driven by the ever-increasing volume and quality of omics studies. Wider EHR adoption and better data warehousing improve the prospects of PregOMICS. With sufficient assurance of ascertainment, PregOMICS studies can also be used to more rapidly identify medications as safe in pregnancy, widening the universe of potential therapies⁴³. Drug repurposing paradigms leveraging molecular and clinical data may produce new candidates for study in pregnancy. The recent trend toward pragmatic clinical trials, in which consent may be waived and outcomes are measured in the normal course of clinical treatment, raises the possibility of low-cost, physician-driven trials that may also positively impact some drugs already in obstetrical use⁴⁴. Indeed, the combination of repurposing drugs known to be safe in pregnancy with newer models of assessing their efficacy may have an important impact on new therapies for diseases in pregnancy.

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Figure 1.

Drug repurposing categorizations. Drug repurposing can occur in 1 of 3 settings. The same drug can be used for the same disease but in a different patient population, such as the use of the same antidepressant in pregnant and non-pregnant patients (top panel). The same drug can be used in a related disease that is specific to a particular population, for example use of nifedipine to treat essential hypertension and hypertension in pregnancy (middle panel). Finally, a drug can be used to treat an apparently unrelated disease in a different population, for example the use of low dose aspirin to prevent coronary artery disease and pre-eclampsia.

Figure 2. The valleys of death

The process from mechanistic study in academic research (left) to successful development and marketing of a drug (Commercial success) has been likened to a valley of death due to the differing financing, culture, and goals of commercial and academic groups. Use in pregnancy adds a second valley of death, in which drugs must demonstrate their safety in this population before wider use is possible.

Figure 3. Example drug repurposing study

This figure represents a 2-pronged strategy for drug repurposing. The first step is to identify drugs safe in pregnancy which have systemic effects with human target genes (e.g. not antibiotics). For the target-based arm, target genes are identified, and the association between those targets and the disease of interest is tested. In the disease-based arm cases and controls are identified, as well as their drug exposure history and demographic information. The overlap between the 2 arms are candidates for repurposing.

Table

Examples of publicly available omics data

Resource	Address	Citation	Downloadable	Comment
Drug targets				
Drugbank	drugbank.ca	20	x	Includes drugs, targets, and indications; recommend 'pharmacological action' subset
Psychoactive Drug Screening Program	pdspdb.unc.edu/pdspWeb/	21	x	Focus on G-protein coupled receptors
Binding Database	bindingdb.org/bind	45	x	
GWAS				
GWAS catalog	ebi.ac.uk/gwas/	28	x	Search-able by gene, variant, or phenotype
UK Biobank	pheweb.sph.umich.edu:5003/	33	x	Web-queryable, good visualizations, includes males and non-pregnant females
	sites.google.com/broadinstitute.org/ukbbgwasresults/home	32	x	Download only, includes males and non-pregnant females
Expression				
PDSP - G-protein expression	kidbdev.med.unc.edu/databases/ShawnCell/home.php	22		Part of PDSP
GTE _x	gtexportal.org	34	login required	Several gestationally informative tissues absent
Human Protein Atlas	proteinsatlas.org	46	x	Protein by IHC and RNA by RNA-seq; Includes placenta but not fetal or gravid tissues
GWAS × Gene expression				
PrediXcan	gene2pheno.org	35		Web query by gene, tissue, or phenotype. Based on GTEX and lacks some tissues
Protein-protein interactions				
String db	string-db.org	47	x	Single protein web query, attractive visualizations
Interologous Interaction Database	ophid.utoronto.ca/ophidv2.204/index.jsp	48	x	Multiprotein web query
BioGRID	thebiogrid.org/	49	x	Visualization tools including multi-protein networks (genemania.org)
Model organisms				
Mouse Genome Informatics	informatics.jax.org	50	x	Not all genes tested; intimidating nomenclature
Online Mendelian Inheritance in Man	omim.org	51	login required	Observational