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Cross-Sectional Analysis of Pregnancy Labeling: When “Limited Data” Unjustifiably Becomes a Global Barrier to Necessary Treatment for Pregnant Women

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Abstract

Prescribing information (PI) serves as the primary regulatory guidance for clinicians treating pregnant women, yet often lacks comprehensive pregnancy data, leading authorities to adopt restrictive language or default contraindications. This cross-sectional study assessed consistency in pregnancy risk communication across five major regulatory authorities: FDA, EMA, TGA, Canada and MHRA. Latest PIs were obtained from official databases of the five regulatory authorities. Only English-language PIs available for at least four authorities were included. Each PI was evaluated for pregnancy contraindications, reported risks (miscarriages, major malformations), and overall tone (permissive/restrictive). McNemar and Fleiss' multi-rater Kappa methods were used to assess the authorities' agreement level. Pregnancy contraindications on EMA, TGA, Canada, and MHRA labels ranged from 18.7%, 20.1%, 23.1%, 21.8%, respectively, versus 7.4% on FDA labels (P<0.001). Restrictive phrasing often appeared despite limited clinical data. Inter-authority agreement was poor for restrictive recommendations (kappa 0.29, 95%CI:0.20-0.38). It appeared more often in EMA (64.5%), TGA (56.7%), Canada (74.5%), and MHRA (60.6%) than in FDA (34.9%) (P<0.001), though references to pregnancy safety data were similar. These inconsistencies reveal regulatory overreach that may deny patients necessary treatments, representing systemic bias against treating pregnant women. The findings underscore the need for harmonized, transparent, evidence-driven regulatory guidance distinguishing “absence of evidence” from “evidence of harm”.

INTRODUCTION

Medication use during pregnancy is highly prevalent; over 88% of pregnant women take at least one prescription or over-the-counter drug.[1,2] Commonly used classes include antibiotics, antiemetics, analgesics, and antidepressants.[3,4] As these drugs are often necessary for managing acute or chronic maternal conditions, delaying or avoiding treatment may have significant risks for both the mother and the fetus.[5–8]

Clinical decision-making regarding medication use during pregnancy requires the consultation of multiple sources of information. Prescribing information (PI), or product label, is one of the primary references for clinicians. Developed by pharmaceutical companies and approved by regulators, the PI provides standardized details on indications, dosage, contraindications, adverse effects, and safety in pregnancy and lactation.[9,10] As such, it plays a central role in promoting the safe and effective use of medications in clinical practice.

Considering the high prevalence of medication use during pregnancy, the accuracy, clarity, and clinical relevance of information in the PI are particularly important. However, generating evidence-based recommendations for this population presents ongoing challenges. Generally, pregnant women are excluded from clinical trials due to ethical and legal concerns. Therefore, most medications are approved without adequate human data regarding fetal or neonatal safety. In the absence of such data, labeling decisions are frequently based on studies examining the reproductive toxicity of drugs in animals,

mechanistic insights, case reports, or post-marketing epidemiological studies. All of which carry limitations when extrapolated to human pregnancy.[9]

Acknowledging the importance of clear and accurate labelling in guiding clinical decision-making, the U.S. Food and Drug Administration (FDA) implemented a significant revision of its pregnancy labelling system in 2015.[11–13] In this reform, the outdated letter-based classification system (categories A, B, C, D, X) was replaced with a more detailed narrative format. Pregnancy and Lactation Labeling Rule (PLLR) contains structured sections including summaries of available data on exposure in pregnancy, risk summary, clinical considerations (e.g., disease-associated maternal and/or embryo/fetal risk), information from both human and animal studies, and effects on fertility. The objective of this revised format was to better reflect the complexity of the underlying evidence and minimize clinicians' misinterpretation.[11–13]

Despite these efforts, recent literature indicates that labeling often remains overly conservative. In many cases, lack of robust data often leads to overly cautious wording, including formal contraindications, even when no direct harm has been demonstrated.[14,15] The lack of clarity may discourage clinicians from prescribing necessary treatments and lead to undertreatment of pregnant and breastfeeding women. Notably, Teratology Information Services (TIS), specializing in providing information on medication safety during pregnancy and lactation, often issues permissive recommendations that directly contradict the official PI language.

This study examined pregnancy safety information in PIs approved by major authorities and evaluated consistency in contraindications, warnings, and recommendations, aiming to promote clearer, evidence-based labeling for pregnant and breastfeeding populations.

METHODS

Study Design and Data Sources

We performed a cross-sectional review of PI documents from five regulators (FDA, EMA, MHRA, Health Canada, TGA) retrieved from official databases (August–September 2024). Only English-language PIs for identical formulations were included; OTC products, supplements, and vaccines were excluded (Appendix 1). For each drug, the most recently approved PI was selected.

Each PI was systematically reviewed by the research team. In cases of ambiguity, classification decisions were made by consensus during weekly meetings.

Extracted data was coded into predefined fields: pregnancy contraindications and warnings, animal data, presence of human clinical data on miscarriage, fetal toxicity, congenital malformations, labor and neonatal effects, fertility, background conditions, class effect, and recommendation phrasing (restrictive or permissive). For each category, it was indicated whether it was mentioned in the text, whether it contained data, and whether the data indicated risk. The categories of miscarriage, fetal toxicity, and

congenital malformations were combined into a single variable, termed Total Pregnancy Risk (TPR), constructed to indicate whether a PI contained data suggesting risk in human pregnancies.

The classification of recommendation language followed the framework established by Kappel et al.[16] Examples of restrictive language include "*Contraindicated in pregnancy*", *"Avoid use"*, and "*Should not be used*". Examples of permissive language include *"May be considered"*, *"Can be used",* and "*Should be used during pregnancy only if the potential benefit justifies the potential risk*". For statistical analysis purposes, in cases where no recommendations were given, i.e., only data was presented and the language could not be interpreted either as permissive or restrictive, it was referred to as permissive language.

Drug Selection

Drugs were selected from the 250 most common medications used by pregnant women in the TIS Zerifin, Shamir Medical Center (Assaf Harofeh), Israel database.[17] TIS Zerifin provides evidence-based guidance on medication and exposure risks during pregnancy and lactation.

The pharmacotherapeutic groups included antibiotics, analgesics, antihypertensives, antiepileptics, and antidepressants. These drug classes have been identified by other TIS centers worldwide as among the most frequent inquiries received during pregnancy consultations.[18–20] Some of these medications are also represented by Polifka et al. among medicines included or considered for inclusion in the World Health Organization's Essential Medicines List.[15] A full list of the included pharmaceutical classes and drugs is provided in Appendix 1.

For the analysis, only drugs with PIs available from four or five regulators were included.

Statistical Analysis

Descriptive statistics were used to summarize the data, with categorical variables presented as numbers (percentages).

McNemar's tests were conducted to assess the statistical association between the paired nominal variables for comparing TPR data with pregnancy contraindications and recommendation language for each regulatory authority. Additionally, inter-authority consistency in pregnancy labeling was assessed using Fleiss' multi-rater Kappa. Inter-authority agreement was interpreted as low (κ = 0.0-0.4), intermediate (κ = 0.41-0.6), or high (κ = 0.61-1.0) based on Kappa values.

Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 28, IBM Corp, Armonk, New York, USA).

RESULTS

Data characteristics

A total of 148 drugs were included in the analysis, each with PIs available from at least four regulatory authorities. The FDA provided PIs for all 148 drugs. EMA had the highest number of missing PIs, with 41 drugs lacking available documents; TGA followed with 9 drugs missing PIs. In Health Canada and the MHRA, only one drug each was missing a PI.

Contraindications

Administration during pregnancy was contraindicated in PIs from EMA, TGA, Canada, and MHRA at a rate of 18.7%, 20.1%, 23.1%, and 21.8%, respectively, compared to FDA labels with only 7.4% of contraindications ($P<0.001$) (Figure 1). Most PIs did not present data suggesting risk of miscarriage, major malformations or fetal toxicity. When assessing the concordance between contraindications and data indicating potential pregnancy risk (TPR, see Methods), the McNemar test demonstrated significant differences in PI between the FDA and TGA ($p<0.001$, $p=0.016$, respectively). No statistical differences were found in PIs from EMA, Health Canada and MHRA (EMA: $p=0.073$, Health Canada: $p=0.44$, MHRA: $p=1.0$) (Figure 2).

Pregnancy-Related Language and Risk Communication

The use of restrictive language in the pregnancy sections of PIs varies significantly among the five regulatory authorities. Health Canada had the highest frequency of restrictive language (74.5% of PIs), followed by the EMA (64.5%), the MHRA (60.6%), the TGA (56.7%), and the FDA (34.9%) ($p<0.001$) (Figure 3).

In Health Canada PIs, restrictive language was applied in 74.5% of cases, while malformation data was provided in 23.8% of cases, fetal toxicity data was provided in only 17.0% of cases. Similarly, EMA PIs included restrictive recommendations in 64.5% of cases, but only 37.4% contained data on congenital malformations, and 25.2% included fetal toxicity data. TGA and MHRA showed similar patterns, with restrictive recommendations appearing in 56.7% and 60.6% of PIs, respectively, while supporting data on any TPR component being available in only 9.5% to 36.5% of cases. FDA PIs included restrictive recommendations in 34.9% of cases, with data on TPR components present in 22.4% to 38.5% of cases (Figures 1 and 3).

The McNemar test was used to assess the degree of agreement between negative TPR data available in PIs and the recommendations language. While no difference at all was found in the FDA ($p=1.0$), all other authorities had significant differences (EMA, Health Canada, and MHRA $p<0.001$, TGA $p=0.002$) (Figure 2). Thus, all regulatory authorities except the FDA demonstrated a statistically significant tendency to impose restrictive recommendations in the absence of risk data.

Inter-Authority Agreement Analysis

Fleiss' multi-rater Kappa analysis revealed poor to moderate agreement between regulatory authorities across most pregnancy safety parameters. Among key safety communication outcomes, agreement levels were particularly poor. These included miscarriage information ($\kappa=0.21$, 95% CI: 0.16-0.26), female

fertility information (κ=0.31, 95% CI: 0.24-0.37), pregnancy warnings (0.40, 95% CI: 0.34-0.46), and overall recommendation phrasing (κ=0.29, 95% CI: 0.20-0.38) (Table 1).

Moderate agreement was observed for contraindications (κ = 0.58, 95% CI: 0.52 to 0.64) and labor newborn effects (κ = 0.60, 95% CI: 0.55 to 0.65). Class effect was the only category marginally having substantial agreement (κ = 0.61, 95%CI: 0.56-0.66) (Table 1).

DISCUSSION

This study reveals significant shortcomings in the way different regulatory authorities communicate medication safety during pregnancy, characterized by the widespread use of formal contraindications and restrictive language on PIs. Health Canada, MHRA, TGA and EMA issued pregnancy contraindications for 18.7–23.1% of the 148 drugs analyzed, nearly three times higher than the FDA rate of 7.4%.

Most PIs lacked meaningful clinical data on key fetal risk outcomes, yet included strong cautionary language. Over 60% of EMA and Health Canada PIs included restrictive terminology, while only less than a third of them referenced major malformations, fetal toxicity, or miscarriages; TGA and MHRA followed the same pattern. Significant P-values in McNemar analyses of restrictive language indicate poor alignment between risk data availability and regulatory wording, reflecting a systematic reliance on precaution over available evidence that may contribute to undertreatment of pregnant women.

Overly restrictive or ambiguous labeling has direct clinical implications. Restrictive phrases have been shown to discourage prescribing and prompt discontinuation of medications during pregnancy. A recent South Korean study revealed that prescription rates for drugs newly labeled as "contraindicated in pregnancy" declined by almost 30% after labeling changes were made.[21] In contrast, in the United States, the 2021 FDA decision to revise its longstanding Category X labeling for statins following a re-evaluation of the literature and the conclusion that the previous contraindication was unjustified led to increased flexibility in prescribing statins to pregnant women at high cardiovascular risk.[22] Both cases were influenced by regulatory language in a direct and measurable manner.

A 2023 qualitative study conducted by Goto et al. in Japan further highlights the significance of clear labeling. The study found that general physicians, who lack special training in pregnancy pharmacotherapy, tended to be overly cautious when prescribing to pregnant women. They were particularly hesitant about drugs labeled as “contraindicated,” even when based solely on animal studies. Alternatively, physicians affiliated with perinatal centers or TISs were more likely to consider medication use in pregnancy safe, particularly when supported by epidemiological data. Across both groups, there was a strong demand for up-to-date, evidence-based PI information that clearly communicates both risks and benefits.[23]

The influence of labeling language extends beyond clinicians to patients as well. Studies from the Netherlands, Australia, and Israel consistently show that pregnant women often discontinue or avoid

necessary medications due to misperceptions of risk, frequently shaped by warnings in PIs and reinforced by advice from healthcare providers or online sources.[24–26] This highlights the widespread impact that labeling language has on real-world prescribing and purchasing behavior and the urgent need to make PIs more clinically meaningful.

Systematically applying the default precaution approach in the absence of strong evidence may carry harmful unintended consequences. Untreated chronic and acute conditions, such as depression, hypertension, epilepsy, autoimmune diseases, and infections, can pose well-documented risks. For example, maternal depression is associated with an increased risk of miscarriage, gestational diabetes, gestational hypertension and preeclampsia, preterm birth, and infants who are small for gestational age. Maternal psychological distress has also been associated with delayed infant neurodevelopment and a higher likelihood of psychiatric disorders in offspring later in life.[8,27,28] In such cases, the harm may result not from the medicinal product, but from communication practices that obstruct informed and necessary clinical care. Therefore, we believe there is an urgent need for risk communication that is both evidence-based and sensitive to the realities of maternal healthcare.

Adding to this challenge is the inconsistency between regulators reviewing the same medications. A physician in the United States may read a label that cautiously advises consultation in pregnancy, while a counterpart in Europe may be faced with an outright contraindication. Both base their practice on the same evidence but receive conflicting regulatory messages, creating confusion among healthcare providers and patients. Some variation may stem from structural differences. The FDA operates as a centralized federal body with a uniform labeling framework, whereas the EMA coordinates across multiple national agencies.[29] However, there is no scientific justification for cross-border PIs discrepancies. Since the medications analyzed in our study were identical in formulation and evidence base, differences in labeling reflect subjective regulatory interpretation rather than scientific disagreement. This erodes confidence in regulatory guidance and reinforces therapeutic hesitation, especially in complex or high-risk pregnancies.

Given these systemic issues, there is a clear and urgent need for reform. One potential approach is to involve expert networks such as the European Network of Teratology Information Services (ENTIS) and the Organization of Teratology Information Specialists (OTIS) in the pre-approval review of pregnancy and lactation sections of PIs. These TISs have extensive experience in evaluating and communicating medication safety during pregnancy and lactation. Their assessments routinely integrate considerations such as the maternal underlying condition, the availability of safer or equally effective alternatives, data from epidemiological studies and case reports, and drug pharmacokinetics in the perinatal period.[30,31] Incorporating TIS expertise into the regulatory process would help ensure that labelling is both evidence-based and actionable. Such collaboration offers a valuable opportunity to bring clinical insight directly into the regulatory process, ultimately promoting pregnant women's well-being.

We also advocate for legislative changes requiring the explicit acknowledgment of data limitations in the pregnancy sections of drug labeling. The ethical imperative to protect fetal health undoubtedly

complicates risk communication in this realm, as conducting research in pregnant populations is inherently challenging. However, excessive caution should not replace transparent communication. In the absence of human data, this should be clearly and transparently stated, for example, by including the phrase “No human data available to assess risk”. Restrictive language such as “contraindicated in pregnancy” should be reserved for cases with robust, consistent evidence of fetal risk. In cases where only animal data are available, the nature of these findings, their relevance to human physiology, and any limitations in extrapolation should be thoroughly explained.

Ultimately, this approach respects the autonomy of clinicians and patients and aligns with international calls for reproductive justice and inclusion in drug development. By implementing these revisions, regulatory communication will be both scientifically based and clinically useful, reducing misinterpretation and improving the quality of care provided to pregnant patients by allowing healthcare professionals to make informed, individualized decisions.

This study has several limitations that should be acknowledged. Although based on a published framework, classification of recommendation language into permissive and restrictive categories may be open to interpretation. It is likely that subtle differences in phrasing and tone may have influenced categorization despite standardized criteria and team consensus. Further, the analysis relied on English-language versions of product labels, which may differ from translated versions in non-English-speaking jurisdictions, and might therefore limit the generalizability of the findings. Additionally, this study focused exclusively on the content of official prescribing information without directly assessing how this language influences practice in the real world. Although existing literature suggests that labeling affects prescribing practices,[17,19,20-22] further research involving clinicians and patients is necessary to confirm the existence of this relationship.

In conclusion, global regulatory authorities recurrently contraindicate or restrict medication use during pregnancy and lactation despite insufficient evidence to justify such caution. This regulatory overreach creates a paradoxical situation where "safety first" policies may actually endanger patients by denying them necessary treatments. When evidence is lacking, authorities should explicitly state "No information is available" rather than defaulting to contraindications that may lead clinicians to withhold beneficial treatments. This pattern of unwarranted restriction represents a systematic bias against treating women during pregnancy and lactation that demands immediate reform.

Declarations

ACKNOWLEDGEMENTS

Figure 2 was generated using Claude (Sonnet 4.5, version claude-sonnet-4-5-20250929), an artificial intelligence software platform developed by Anthropic PBC, San Francisco, California, based on data and specific instructions provided by the authors.

AUTHOR CONTRIBUTIONS

N.BK., O.C., M.B., and M.BERK. wrote the manuscript; E.K., N.BK., O.C., M.B., M.BERK., S.S., S.Y, T.DH., and A.H. designed the research; N.BK., O.C., E.K., S.Y., T.DH., A.H., M.B, M.BERK. and S.S. performed the research; M.B., E.K., N.BK., O.C. and S.Y. analyzed the data. N.BK. and O.C. contributed equally to this work. All authors discussed the results and approved the final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

MATERIALS & CORRESPONDENCE

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Tables

Table 1: *Level of agreement between Regulatory Authorities*

Pregnancy Category	KAPPA Value[a,b]	Range[b] (95% CI)	Agreement level
Miscarriage	0.21	(0.16-0.26)	Low
Animal data	0.24	(0.18-0.30)	Low
Development	0.25	(0.20-0.30)	Low
Recommendation phrasing	0.29	(0.20-0.38)	Low
Female fertility	0.31	(0.24-0.37)	Low
Background conditions	0.31	(0.26-0.40)	Low
Major malformations	0.38	(0.33-0.43)	Low-intermediate
Labor maternal effects	0.40	(0.34-0.45)	Low-intermediate
Pregnancy warning	0.40	(0.34-0.46)	Low-intermediate
Fetal toxicity	0.51	(0.47-0.56)	Intermediate
Pregnancy Contraindication	0.58	(0.52-0.64)	Intermediate
Labor newborn effects	0.60	(0.55-0.65)	Intermediate
Class effect	0.61	(0.56-0.66)	High-intermediate

[a] The Kappa value ranges from 0.0 to 0.4, indicating a low level of agreement between the five regulatory authorities. A Kappa value of 0.41-0.60 indicates intermediate levels of agreement among the authorities. A Kappa value of 0.61 to 1.0 indicates a high level of agreement within the authorities.

[b] Calculated by McNemar and Fleiss' multi-rater Kappa methods.

Figures

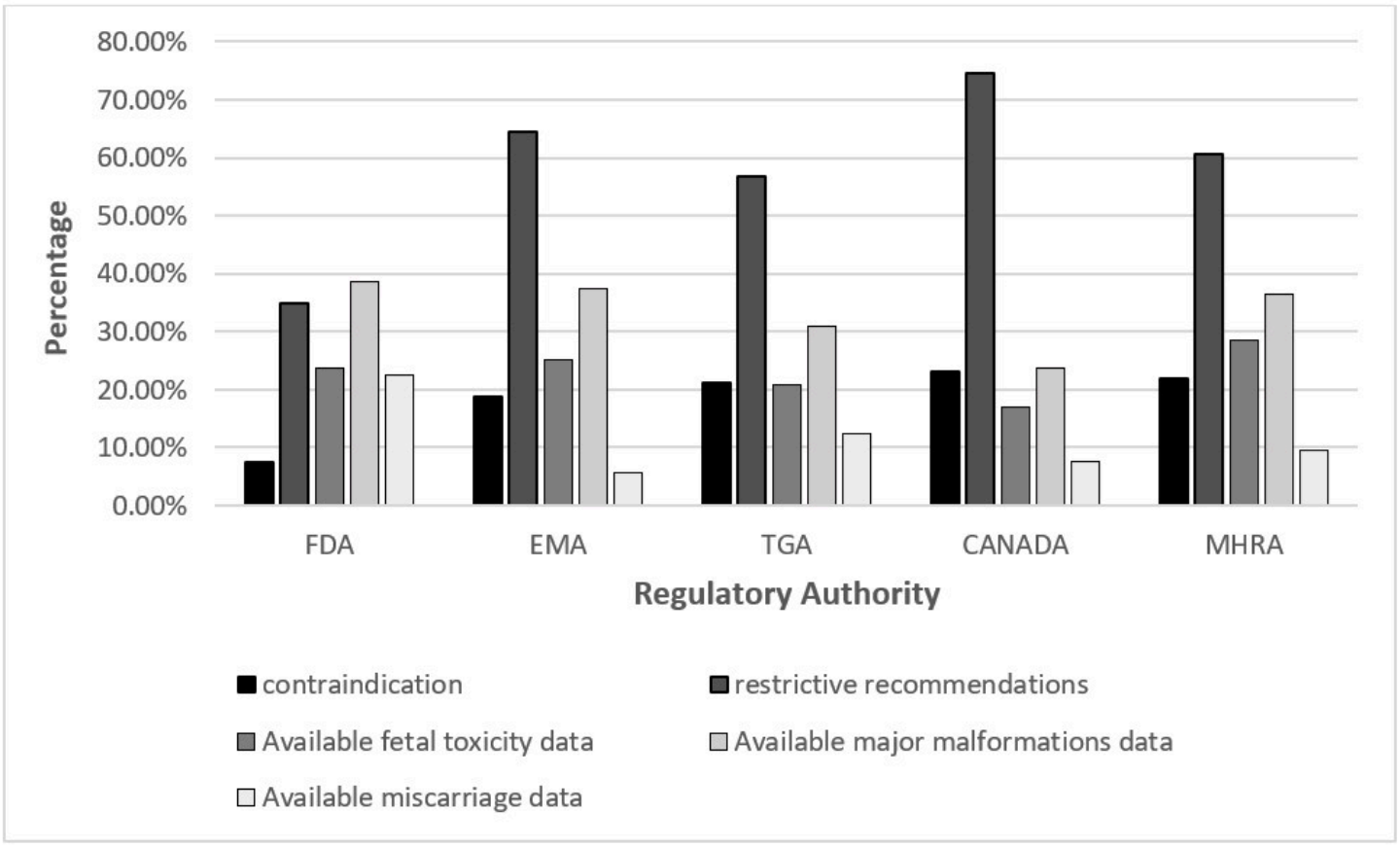


Figure 1

Safety Data on Pregnancy Risks, Restrictive Language, and Contraindications in Prescribing Information

[a] Data are presented for 148 drugs' prescribing information obtained from five regulatory authorities. Percentages indicate the prevalence of each parameter among the prescribing information reviewed within each authority.

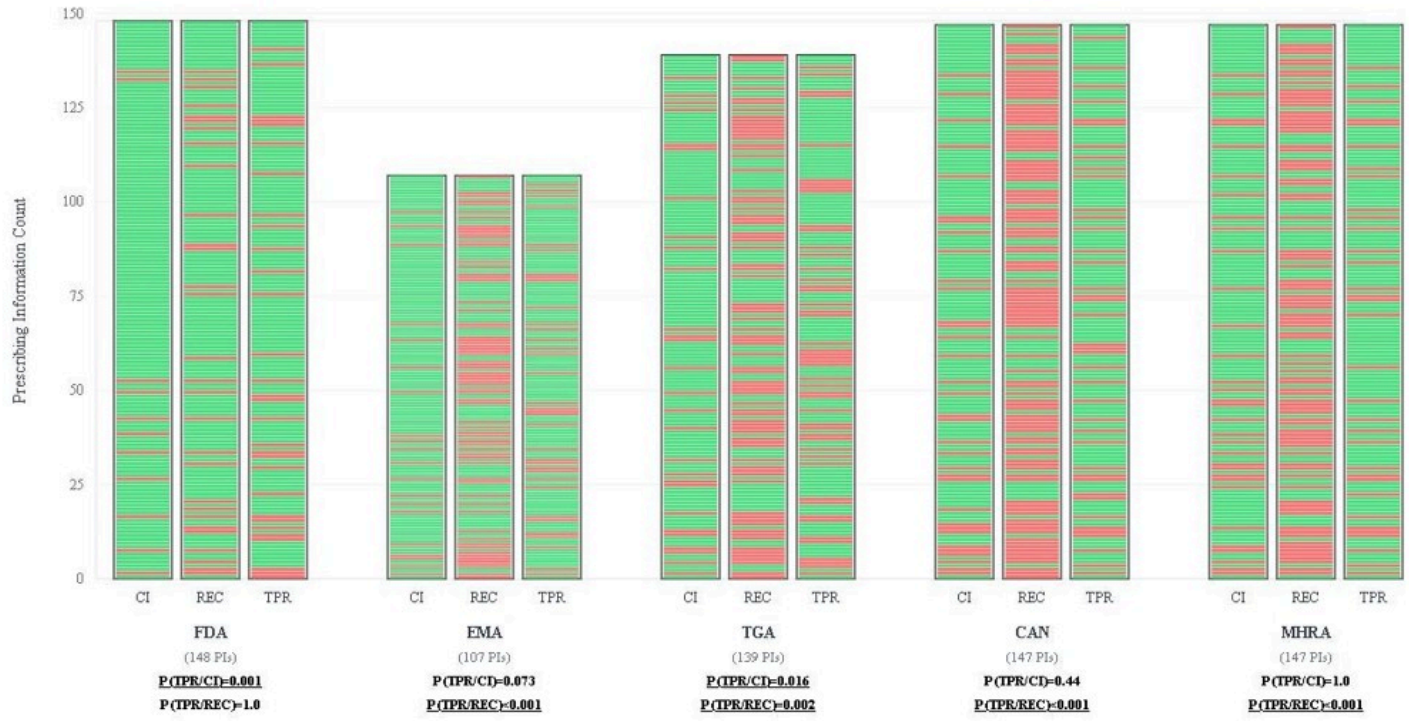


Figure 2

Disproportionate use of contraindications and restrictive language relative to available fetal risk data presented as Total Pregnancy Risk (TPR)

[d]Abbreviations: CI = contraindication; Rec = recommendation; TPR = Total Pregnancy Risk.

[a] Each row of lines represents a single drug (prescribing information).

[b]Green lines indicate no negative information. For TPR, a green line shows that no negative data were reported for any of the three categories (miscarriage, congenital malformations, fetal toxicity). For CI, a green line indicates no pregnancy contraindication. For recommendations, a green line indicates permissive language.

Red lines indicate negative information. For TPR, a red line shows that negative data were reported for at least one of the three categories. For CI, a red line indicates a pregnancy contraindication. For recommendations, a red line indicates restrictive language.

[c] P values Calculated by McNemar test.

[d]Abbreviations: CI = contraindication; Rec = recommendation; TPR = Total Pregnancy Risk.

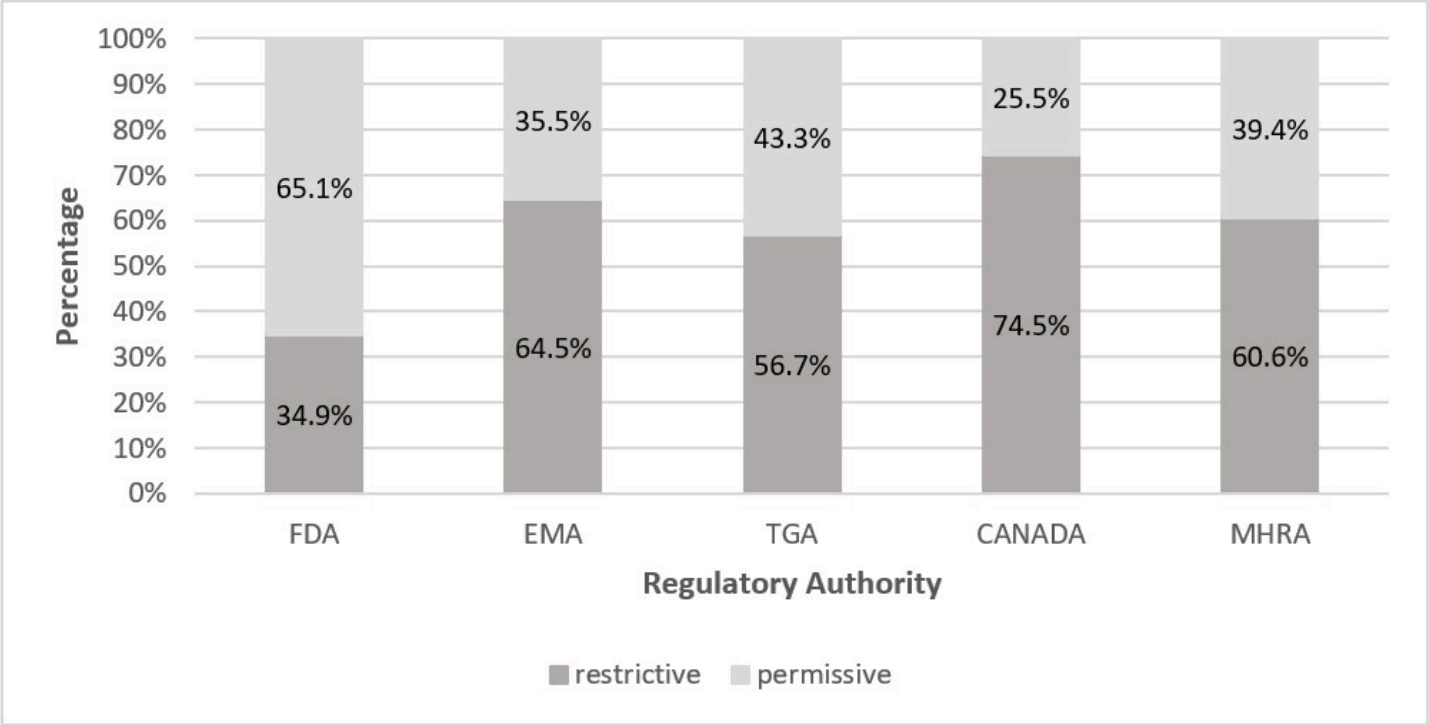


Figure 3

Pregnancy Risk Communication Language Across Regulatory Authorities

[a] Data is presented for 148 drugs' prescribing information obtained from five regulatory authorities. Analyses are based on the number of drugs available in each authority (FDA, 148; EMA, 107; TGA, 139; Health Canada, 147; MHRA, 147).

Supplementary Files

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