

REMS in pregnancy: system perfectly designed to get the results it gets

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Reproductive drug safety has been a priority for patients and physicians even before the 1960s, when thalidomide—a drug commonly used to alleviate morning sickness—was tied to alarming cases of infants born with phocomelia.¹ The Kefauver-Harris Amendment of 1962 prevented thalidomide approval in the USA.¹ The legislation also led to immediate reforms in how drugs were approved, but not necessarily *how* they were prescribed.¹ In the decades that followed, processes to regulate safe prescribing lagged.

The first reproductive drug safety initiatives were those for isotretinoin (Accutane) and thalidomide: the Accutane Pregnancy Prevention Program (1988), the System for Thalidomide Education and Prescribing Safety (1998) and the System to Manage Accutane-Related Teratogenicity (2002). In response to persistent gaps in these and other drug safety monitoring programmes, the US Food and Drug Administration (FDA) subsequently implemented the Risk Management and Evaluation Strategy (REMS) programme in 2007.² REMS is a multifaceted programme intended to ensure prescribing and dispensing of specific drugs occur only in situations in which the potential benefits outweigh the potential risks.² The best known REMS is iPLEDGE, which aims to regulate isotretinoin in pregnancy.

Each REMS has key components, including medication guides, product inserts and communication plans, informing healthcare providers and professional societies about drug harms. Additional components called elements to assure safe use (ETASU) apply to drugs with the most significant safety concerns, and include training and certification programmes for physicians and

pharmacists, laboratory monitoring, creation of drug registries and restrictions on distribution (eg, hospitals and infusion clinics). The REMS programme was also intended to provide a means of evaluating the efficacy and efficiency of drug safety monitoring programmes.

Today, 57 active REMS programmes are approved by the FDA, 10 of them pertaining to drugs in pregnancy (table 1).³ It is important to note that while similar programmes exist in other jurisdictions, REMS only apply to drugs in the USA. These initiatives are undoubtedly well-intentioned, but in reality, they are controversial and expensive. In some circumstances, REMS may compromise patient care by discouraging the prescribing of drugs with clear benefit. REMS are also cumbersome for pharmacists, manufacturers and drug distributors, and require extensive administrative resources. Consequently, REMS only make sense if they improve drug safety to an extent that outweighs the burdens they create.

In this issue of *BMJ Quality & Safety*, Sarayani *et al*⁴ examine the real-world effectiveness of implementing the REMS for mycophenolate, an immunosuppressant drug commonly used for solid organ transplant recipients and patients with autoimmune diseases. Mycophenolate should be avoided in pregnancy because of its association with first-trimester loss and an increased risk of congenital anomalies.⁵ The most frequent malformations associated with mycophenolate are cleft lip and palate, anomalies of the external ear and other facial defects.⁵ One study of 26 pregnancies exposed to mycophenolate identified 11 spontaneous abortions (42%) and 4/15 (27%) live-born infants who had structural



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Table 1 Risk Evaluation and Mitigation Strategies (REMS) for drugs in pregnancy

Drug	Clinical indication	Fetal effects	ETASU
Riociguat (Adempas)	Pulmonary arterial hypertension	Preclinical animal studies demonstrated increased pregnancy loss and congenital cardiac defects.	Yes
Ambrisentan (Letairis)	Pulmonary arterial hypertension	Preclinical animal studies demonstrated cardiopulmonary, facial and thyroid congenital defects.	Yes
Bosentan (Tracleer)	Pulmonary arterial hypertension	Preclinical animal studies demonstrated cranial, orofacial and cardiopulmonary congenital defects.	Yes
Isotretinoin (Accutane)	Cystic acne	Congenital defects of the face, ears, heart and brain	Yes
Mycophenolate (Cellcept and Myfortic)	Solid organ transplant and autoimmune disease	Congenital defects of the face and ears	Yes
Macitentan (Opsumit)	Pulmonary arterial hypertension	Preclinical animal studies demonstrated cardiac and orofacial congenital defects.	Yes
Pomalidomide (Pomalyst)	Multiple myeloma	Preclinical animal studies suggest congenital defects similar to those caused by thalidomide.	Yes
Lenalidomide (Revlimid)	Multiple myeloma	Preclinical animal studies suggest congenital defects similar to those caused by thalidomide.	Yes
Thalidomide (Thalomid and Celgene)	Multiple myeloma	Phocomelia and other congenital defects	Yes
Topiramate+phentermine (Qsymia)	Weight loss	Orofacial defects	Yes

ETASU, elements to assure safe use.

malformations.⁶ In 2012, the FDA approved a REMS for all mycophenolate products, which includes an ETASU.⁷

Using a database of private health insurance claims in the USA, Sarayani *et al* used a pre-post study design to examine mycophenolate exposures in patients 15–44 years old before and after the REMS implementation.⁴ The outcomes of interest were twofold: (1) the period prevalence of mycophenolate initiation in pregnant women and (2) rates of conception while receiving mycophenolate. Compared with the period prior to REMS initiation, Sarayani *et al* found fewer mycophenolate exposures in pregnancy after REMS (4.2 per 1000 treatment episodes vs 1.9 per 1000 treatment episodes), but no difference in the incidence of new pregnancies in women already taking mycophenolate (13.1 new pregnancies per 1000 years of treatment pre-REMS vs 12.1 per 1000 years post-REMS).⁴ This pattern suggests that the REMS for mycophenolate prevented new drug starts in pregnant women but did not stop women already taking it from becoming pregnant.

The observed change in mycophenolate prescribing may not be solely due to the implementation of the REMS. Pre-post studies such as this are susceptible to cointerventions, residual confounding and temporal changes that may have occurred even without an intervention.⁸ Failing to account for temporal confounding—sometimes referred to as ‘history bias’—can lead investigators to draw erroneous inferences about the effect of an intervention.^{8,9} An alternate approach Sarayani *et al* could have used to characterise the extent to which temporal confounding occurred would have been to also examine outcomes

in a control drug (or drugs) not expected to be influenced by the REMS for mycophenolate.⁸

Studies examining the effect of REMS for other drugs have yielded similar results. In a retrospective observational study of over 8000 women who filled a prescription for isotretinoin, there were no differences in rates of fetal exposures in women of reproductive age before and after implementation of iPLEDGE.¹⁰ A second study demonstrated that rates of coprescriptions of isotretinoin with contraception (oral formulations, transdermal patches, implants, injectables and intrauterine devices) increased by only 1.2% following iPLEDGE.¹¹ Furthermore, a recent study showed an overall decrease in frequency of pregnancies, fetal defects and abortions in women taking isotretinoin following implementation of iPLEDGE.¹² However, the number of reports of isotretinoin-related adverse pregnancy outcomes peaked prior to iPLEDGE in 2006, while significant changes were not observed until 5 years later.¹² If iPLEDGE were solely responsible for the change in outcomes, a decrease would have been expected shortly after implementation. While studies examining the effect of the lenalidomide and thalidomide REMS have yielded more promising findings, they may have been destined to succeed because these drugs are indicated for the treatment of multiple myeloma, a disease that typically does not affect women of reproductive age.¹³

Although REMS may have a more substantial impact on drug safety than initially observed, poor data quality and study limitations preclude proper evaluation.² Since inception in 2007, there have been significant shortcomings in the data examining individual REMS because the FDA does not have the

authority to require data submission.¹⁴ In 2013, the inspector general of the department of health and human services concluded that the benefits of some of the REMS were uncertain.¹⁵ For more than one-third of REMS, an accurate determination of efficacy was not possible, owing to the lack of reliable methods to properly evaluate implementation.¹⁵ In January 2019, the FDA announced a commitment to studying their real-world effectiveness through new standardised protocols for developing REMS assessment plans and provided guidance on conducting surveys to assess patient and provider knowledge of REMS-related information.¹⁶ Such interventions may ultimately improve our ability to determine the effect of REMS on clinically important outcomes.

An alternative possibility is that REMS is not as effective as originally hoped. This is particularly concerning in the setting of reproductive drug safety because a single teratogenic exposure is one too many. However, preventing pregnancy in women taking potentially teratogenic drugs is not easy. It requires awareness from both patient and prescriber, relying heavily on contraception. While REMS indeed emphasise (and in some cases mandate) effective contraception, decisions in that regard obviously rest with patients. Access and adherence are also affected by patients' ability to pay for contraception, and willingness of healthcare providers to assist them in finding methods that suit their lifestyles and preferences. Moreover, while the use of contraception is ultimately a choice, even with impeccable adherence, no method is fail-safe.

In the case of isotretinoin, the most common reason for pregnancy while enrolled in the iPLEDGE programme is failure of contraception or non-compliance with birth control.¹⁷ Another potential contributor is that contraception is inadequately prescribed and used by women taking teratogenic drugs. Studies have demonstrated that among women taking potential teratogens, less than one-third receive appropriate contraception.^{18 19} An important but sobering finding of the study by Sarayani *et al* was the similar rates of contraceptive use among women preimplementation and postimplementation of the REMS for mycophenolate.⁴ Unplanned pregnancies are, unfortunately, a clinical reality, even during treatment with a known teratogen.

Most REMS programmes that aim to restrict drug use in pregnancy focus on education. Anecdotally, providers report that when pregnancies do occur, they were unlikely to have been prevented by written protocols and guidelines.²⁰ Patients feel that REMS such as iPLEDGE are anxiety-provoking, focus too heavily on teratogenicity, and lack appropriate guidance on effective contraception.²¹ Therefore, one solution might be to allocate resources to helping patients access safe, affordable and effective contraception. An additional strategy might be to encourage methods of long-acting reversible contraception such as intrauterine devices.

REMS may exemplify the adage 'the system is perfectly designed to get the results it gets'. While entwined with reproductive drug safety, the efficacy of REMS may be more perception than reality. Creating regulatory safeguards is crucial, and REMS may be only one part of a larger solution that strives to engage and educate patients, prescribers, regulators, and industry about reproductive drug safety. Moreover, while devising methods to study REMS is a priority for the FDA, a more pressing issue is finding innovative ways to protect mothers and babies from unsafe drug exposures in pregnancy.

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