Pharmacotherapy

https://doi.org/10.1038/s41684-024-01374-7

Evaluation of lipid nanoparticles for safe and efficient RNA delivery during pregnancy

Lipid nanoparticles (LNPs) have recently emerged as one of the most advanced technologies for RNA delivery, particularly for vaccination against COVID-19. Clinical trial data suggest that COVID-19 mRNA vaccines are safe during pregnancy, opening the door to new therapeutic options for pregnant individuals. A new study in *PNAS* provides additional evidence that LNPs can safely deliver mRNA to the placenta and maternal organs without harming the fetus.

First, the investigators evaluated in vitro the efficacy and toxicity of an LNP library. The results show that while the ionizable lipid headgroup was a major determinant of mRNA delivery potency, the lipid tail LNP governed the hemolytic activity.

Next, the team selected LNPs that did not show in vitro hemolytic activity and injected them intravenously in pregnant mice, together with bioluminescent or fluorescent reporters. When assessing LNP biodistribution using an in vivo imaging system (IVIS), the team observed that LNPs accumulated in the placenta and in various non-reproductive organs of the dam, such as the liver and the spleen, but not in the fetus.

The investigators also tested different administration routes, including intramuscular and intraperitoneal injections. They showed that although the delivery route impacted organ tropism and overall efficacy in pregnant mice, no route of administration produced luminescence in the fetus.

Further experiments revealed that LNP immunogenicity was a critical factor for LNP tropism and safety. More specifically, pregnancy altered organ tropism for immunogenic lipids but not for immunoquiescent lipids. In addition, compared with immunoquiescent lipids, immunogenic lipids prompted an innate immune response in mice and increased B and T cell infiltration in the placenta. Finally, although no dam or pup mortality occurred after LNP administration, pup monitoring revealed that immunogenic LNPs slowed pup growth.

Altogether, this study provides useful guidance for the design of LNP-based therapies during pregnancy and suggests that safe immunoquiescent LNPs could be employed for several prophylactic and therapeutic applications in pregnant individuals, including for treating preeclampsia.

Alexandra Le Bras

Original reference: Chaudhary, N. et al. *Proc. Natl Acad. Sci. USA* **121**, e2307810121 (2024)