

# Prevention of COVID-19 in pregnant women, eventual use of new vaccines

## Prevención de COVID-19 en las gestantes, eventual uso de las nuevas vacunas

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### SUMMARY

*Pregnant women who have COVID-19 have an increased risk of hospitalization and death; however, there are many restrictions for the application of COVID-19 vaccines on pregnant patients, mainly because there is no confirmation of the safety of their use during pregnancy. None of the vaccines approved to date are based on live attenuated SARS-CoV-2, so the possibility of generating an infection in the fetus is nonexistent. Likewise, current evidence does not suggest that COVID-19 vaccines can induce a complication or adverse pregnancy outcome and due to the emergence of new waves of COVID-19, the potential protective benefits of these vaccines far outweigh the possible risks in most patients. A*

*review of the evidence of the safety of COVID-19 vaccines, recommendations, and restrictions for the use of COVID-19 vaccines in pregnant women made by international health organisms and professional associations, as well as prospects and information on clinical trials of these vaccines in pregnant women are presented.*

**Keywords:** Vaccine, pregnancy, COVID-19.

### RESUMEN

*Las gestantes con COVID-19 tienen un riesgo aumentado de hospitalización y muerte, sin embargo, existen muchas restricciones para el uso de las vacunas contra esta enfermedad en este tipo de pacientes, principalmente porque no se dispone de confirmación de seguridad de su uso durante el embarazo. Ninguna de las vacunas aprobadas hasta la fecha se basa en el*

DOI: <https://doi.org/10.47307/GMC.2021.129.2.15>

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**Recibido: 7 de abril 2021**

**Aceptado: 23 de abril 2021**

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*virus SARS-CoV-2 atenuado, por lo que la posibilidad de generar una infección en el feto es prácticamente nula, asimismo, la evidencia actual no sugiere que estas vacunas puedan inducir una complicación o resultado adverso del embarazo y dada las circunstancias de nuevas olas de COVID-19, los potenciales beneficios de protección de estas vacunas sobrepasan ampliamente los posibles riesgos en la mayoría de las pacientes. Se presenta una revisión sobre la evidencia de la seguridad de las vacunas disponibles en Venezuela contra el COVID-19, y las distintas recomendaciones sobre la aplicación de vacunas anti-COVID-19 en gestantes hechas por las agencias, organismos internacionales de salud y asociaciones profesionales, así como las perspectivas futuras e información sobre ensayos clínicos de estas vacunas en gestantes.*

**Palabras clave:** *Vacunas, embarazo, COVID-19.*

## INTRODUCTION

Although several months have passed since the emergency approval of the first COVID-19 vaccine (1), its use has still not been recommended on pregnant women (2), mainly because there is no confirmation of the safety of their use in this kind of patients (3). However, pregnant women urgently need this kind of protection during this pandemic because they are at a higher hospitalization and death risk when they get infected with COVID-19 (42). Taking this into account, many specialists do not agree with delaying the immunization of pregnant women since, although there is no information derived from clinical trials in these patients, there is also no indication or evidence to suggest that the available COVID-19 vaccines may cause a complication or adverse pregnancy outcome (5).

In this article, we present a review of the available evidence regarding the safety of the vaccines against COVID-19, the different recommendations about the application of the vaccines anti-COVID-19 in pregnant women made by the agencies, international health organizations, and professionals associations, as well as the future perspectives and information about a clinical trial of these vaccines in pregnant women.

We hope that this document may help health professionals (and their patients) to decide the administration of vaccines against COVID-19 on

pregnant women, based on proven data.

### Is it safe to vaccinate pregnant women?

The risk/benefit assessment rules any decision for the administration of the vaccine during pregnancy, therefore, for some diseases, it is not only safe to vaccinate the pregnant women, but it is an important recommendation, as such vaccines prevent diseases of high incidence and causal of complications during pregnancy, such as the vaccines against influenza y pertussis (6,7).

It is a consensus that the inactivated or subunits vaccines are safe in pregnancy, while it is preferred to avoid vaccines with attenuated microorganisms due to potential infection of the fetus (7,8).

There is a generalized recommendation for the application of the inactivated vaccine against influenza in any trimester of pregnancy (9,10), as it decreases the possibility of acquiring this infection, which can generate important complications in the pregnant woman, besides the protection it provides for the newborn by the transference of passive immunity through the lactation (11).

It is logical to think that the application of COVID-19 could similarly protect pregnant women as influenza vaccines do, i.e., reducing the risk of infection, preventing aggravation of the patient as a consequence of the infection, and providing passive immunity to the newborn.

Other advantages of vaccination against COVID-19 in pregnant women are the potential to contribute to the development of herd immunity and to reduce the risk of infection to obstetricians and gynecologists.

### Guidelines of the international health organizations and associations

By the time of writing this article, the positions of the major health agencies and organizations on the use of COVID-19 vaccines in pregnancy are heterogeneous.

The World Health Organization (WHO) prudently states although there is no evidence that the vaccines against COVID-19 may generate some health inconvenience during pregnancy, it is recommended that only those pregnant women with high exposure to SARS-CoV-2 risk or those with other comorbidities are to receive

de administration of the vaccine after consulting with their physician (2).

A similarly prudent position is that of the European Medicines Agency (EMA) when suggesting that the decision for administering, or not, the vaccine to the pregnant woman shall be taken with the advice of a health professional after the evaluation of risks and benefits (12).

The Control of Disease Center (CDC) of the United States of America has a more open position claiming that “Any of the currently authorized COVID-19 vaccines can be offered to people who are pregnant or breastfeeding” (5), as probably have information derived from the experience of the application of the vaccines to 20 000 pregnant women without the generation of any inconvenience or “red flag” as appointed by Dr. Anthony Fauci (13).

This position of the CDC is very close to that of the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) by finals of 2020, they advocate for the inclusion of pregnant women in the clinical trials of the vaccines against COVID-19 and offer the vaccine against COVID-19 to all pregnant women (14,15).

Likewise, the Health Ministry of Israel, one of the countries that currently have the highest coverage of vaccination against COVID-19, on 20 January issued the recommendation of the vaccination with no restriction of pregnant women (16), being probably the first country to do so.

Recently, the Japan Society for Infectious Diseases in Obstetrics and Gynecology (JSIDOG) and the Japan Society of Obstetrics and Gynecology (JSOG), published a comprehensive list of recommendations regarding the use of the COVID-19 vaccines in pregnant women (17).

In their document JSIDOG and JSOG recommend the application of COVID-19 vaccines to pregnant women, but also suggest other novel recommendations such as: avoid the vaccination during the first 12 weeks of pregnancy, application of the respective vaccines to husbands or couples, and other family members that live in the same home, the vaccination of the pregnant woman shall be in the obstetric visit to verify the fetus heart movement before and after

the administration, and vaccination of obstetrician and obstetric sanitary personnel (17).

As long as there is more information available derived from clinical studies, the recommendations will be widened the use of the COVID-19 vaccine in pregnant women.

### **Is it safe to administer the COVID-19 vaccines available in Venezuela during pregnancy?**

During this pandemic, a huge amount of false information has been circulating on social networks, and the vaccines against COVID-19 have been one of the preferred subjects of the authors of such “Fake news”. Therefore, the purpose of this article is to objectively show the benefits that the different vaccines against COVID-19 can provide to pregnant women and their babies and to refute information that lacks scientific evidence.

**Adenoviral vector vaccines:** Based on non-replicative adenoviruses (AdV) modified by genetic engineering to eliminate the genes necessary for replication and to introduce the S gene that encodes the SARS-CoV-2 spike protein (18).

This kind of platform of modified adenovirus has been studied and developed for more than three decades and has its origin in genetic therapy assays (19). Adenoviruses are a family of naked, double-stranded DNA viruses that infect humans, and other animals (20). In humans, it causes auto-limited diseases such as cold, gastroenteritis, conjunctivitis, among others (20).

The adenoviruses, unlike other viruses such as retroviruses (21) and Adeno associated viruses (AADV) (22), lacks the genetic machinery necessary for integration in the host cell genome (23), this provides them a good safety profile that has been extensively evaluated (20). The possibility of prolonged persistence of the genetic material of the adenoviral vector or the integration to the host cell genome is extremely low (23).

Adenoviruses cause lytic infection upon replication in host cells (24), the absence of replicative capacity of the vaccine vectors contributes to the safety of the vaccine, therefore, it should not present a potential risk to the fetus.

In the past, successful clinical trials have been

performed in pregnant women with a vaccine platform based on the human adenovirus type 26 (Ad26), actually used in the Ad26.COVS vaccine of Janssen/Johnson & Johnson against COVID-19. The trials using the Ad26 platforms for vaccines against Ebola and AIDS applied in more than a thousand pregnant women suggested that there are no safety issues during its use in this stage (25).

There is also a report with positive results in a small group of women that got inadvertently pregnant during the assay of the Oxford/AstraZeneca vaccine in the United Kingdom. The study showed that there is no difference between the spontaneous abortion rates between the vaccinated pregnant women group and those in the placebo group, which suggests that there is no harmful effect of the vaccination in the initial stages of the pregnancy (26).

There is currently available in Venezuela a vaccine of this kind, the Sputnik V or Gam-COVID-Vac, which uses two adenoviral vectors rAd26 and rAd5. Its use in Venezuelan pregnant women is restricted, there is also the intention of bringing to Venezuela the Ad26.COVS vaccine through the COVAX mechanism (27), it is unknown if it would be used on pregnant women.

Vaccines with virus subunits and inactivated virus. In theory, these vaccines against COVID-19 should be safe during pregnancy, however, right now, none of them has been authorized for its use during pregnancy, nor in the origin countries, China, India, or Cuba (28,29), nor in the receptors of the vaccines countries (30,31).

The basis of the available inactivated vaccines is the replication of a SARS-CoV-2 strain in Vero E6 cells, then the virions are harvested, inactivated with beta-propiolactone, and absorbed with aluminum salts that serve as an adjuvant. The vaccines of the Chinese laboratories Sinopharm (32), Sinovac (33) and the Hindu vaccine Covaxin (34,35) follow these manufacturing principles with few differences among them.

The use of aluminum salts as an adjuvant is a common practice in many inactivated vaccines but has several problems in the context of the vaccines against COVID-19. The aluminum

salts are inefficient stimulators of T cells (36), so a robust cellular response is not obtained with this type of vaccine, moreover, the cellular response induced by this vaccine is biased to a Th2 cytokine profile, which can be counterproductive in COVID-19 (37).

A vaccine that elicits a Th2 response associated with certain antigens of SARS-CoV-2 such as the nucleocapsid (N) protein could lead to the induction of enhanced respiratory disease (ERD) upon subsequent infection with this virus (37,38).

The Covaxin vaccine produced by Bharat Biotech laboratory has an additional feature: in addition to the aluminum salts, it presents as adjuvant an imidazoquinoline molecule called IMDG, which is an agonist of Toll-like 7 and 8 receptors (39). The presence of this IMDG improves the immunogenicity of the vaccine and induces a Th1-biased immune response, which is ideal in a vaccine against COVID-19 (34).

Very little is known about the Cuban candidate vaccines against COVID-19, but it has been announced by the government that in the upcoming months, a large proportion of the Venezuelan population will receive a "massive" vaccination with the Cuban candidate vaccine Abdala (40). It is known that this subunit vaccine is composed of a small portion of the protein S against which the principal neutralizing antibodies are targeted, the RBD (*receptor-binding domain*) absorbed to aluminum salts as an adjuvant (41).

There are several specific inconvenient with the use of Abdala under the conditions proposed to vaccinate the Venezuelan population. At the time of writing this text, it is still in clinical trials; phase 3 should just be starting (41), therefore, planning a mass vaccination without the certainty that the vaccine candidate can successfully pass this phase 3 is premature; also, the results of the previous preclinical studies and the previous phases 1 and 2 of this vaccine candidate are unknown; in this regard, the National Academy of Medicine has warned about these inconvenient in several bulletins (42).

There is three other potential inconvenient with this vaccine candidate, one is the use of aluminum salts as an adjuvant, which as previously mentioned could generate a Th2

response that is not protective but rather causes ERD in successive encounters with the virus (37), in addition, although most of the neutralizing antibodies against SARS-CoV-2 are directed against the RBD, there are also neutralizing antibodies directed against other regions of the S protein such as the N-terminal domain (NTD) (36) and the fusion peptide (43), which would not be induced by this vaccine and which would be very important to compensate the loss of vaccine efficacy due to mutations in the RBD such as E484K in variants such as B.1.351 and P.1/B.1.1.1.28 which are increasingly prevalent in Latin America.

Finally, the administration of this vaccine candidate in each patient needs three separated time dosages (41), which complicates the logistics of the vaccination, increases the expenses, the time for reaching the full deployment of the vaccines, and could promote de desertion of the patients.

A summary of the characteristics of the COVID-19 vaccines that are planned to arrive in Venezuela is shown in Table 1.

In conclusion, the inactivated vaccine that is available in Venezuela, Sinopharm Vero Cell, despite not being authorized for its use on pregnancy, and no studies are supporting its safety at this stage, could be used in this group of patients after the risk/benefit assessment and keeping in mind the possibility of infection of the fetus with the components of the vaccine is not possible. The follow-up of the immunized women to confirm the safety and monitor any ERD event that could arise is suggested.

### Future perspectives and conclusions

While more information about vaccine safety is obtained through clinical trials and cohort studies of vaccinated pregnant women, the recommendation of the administration of the vaccines to this group of patients would be widened.

However, none of the recent studies suggests the occurrence of some type of problem that can put at risk the pregnancy as a consequence of the administration of some of the vaccines against COVID-19. The current evidence suggests that

Table 1  
List of COVID-19 vaccines planned for Venezuela

| VACCINE                       | PLATAFORM PUBLISHED    | EFFICACY FOR USE IN PREGNANCY | RESULTS | APROVED                 | ARRIVAL TO VENEZUELA   |
|-------------------------------|------------------------|-------------------------------|---------|-------------------------|------------------------|
| Sputnik-V                     | Adenoviral Vector      | 91 %                          | Phase 3 | NO                      | FEBRUARY 2021          |
| Vero Cell - Sinopharm         | Inactivated SARS-CoV-2 | 79 % (?) <sup>1</sup>         | Phase 2 | NO                      | MARCH 2021             |
| Ad26.COV2.S - Johnson&Johnson | Adenoviral Vector      | 66.3 %                        | Phase 3 | YES, (USA) <sup>2</sup> | JULY 2021 <sup>3</sup> |
| Abdala-CIGB CUBA              | Subunit Vaccine        | ?                             | None    | NO                      | JULY 2021              |

<sup>1</sup>Claimed efficacy in phase 3 trials, results not yet published.

<sup>2</sup>CDC Information about COVID-19 vaccines for people who are pregnant or breastfeeding.

<sup>3</sup>Subject to approval, according to COVAX program.

these vaccines are sufficiently safe, immunogenic during pregnancy (44) and are capable of inducing immunity that can be transmitted to the newborn through the placenta (44,45) and the breastfeeding (44).

The results of an ongoing clinical trial of the Comirnaty™ vaccine of Pfizer/Biotech in 4 000 pregnant women (46) will be the key for future indications of immunization.

Meanwhile, everything indicates that the vaccination against COVID-19 must be offered to pregnant women, as long as the immunization is performed with vaccines that do not contain the attenuated SARS-CoV-2 and are approved by reliable regulatory agencies. The use of vaccine candidates is not recommended in pregnancy.

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