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Effect of SpikoGen subunit vaccine administration during pregnancy on fetal development of rats

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Purpose: The effects of coronavirus disease 2019 vaccination on fertility and pregnancy have turned out to be a main topic of public attention. Inactivated or recombinant protein vaccines are a reliable and safe method but mostly suffer from weak immunogenicity just in case formulated with a suitable adjuvant. The purpose of this research was to assess the impacts of new SpikoGen subunit vaccine administration during pregnancy on organogenesis in the rat fetus, which is a novel achievement in teratogenesis studies.

Materials and Methods: In the first group (G1) animals received normal saline. A dose of 25 μg of the vaccine was administered to groups of rats as follows: groups 2, 3, 4, and 5 received two doses of vaccine on different days before and after start of pregnancy. On day 21, after the caesarean process, the effects of the vaccine were estimated by morphological, skeletal, and histological studies.

Results: Administration of the SpikoGen vaccine had no significant effect on weight, head diameter, tail length, and length of the fetuses to their tail. There were no malformations, toes and legs were fully developed, and all internal organs of the fetus were completely formed. Also, there was no difference in the overall skeletal opacity and density between the control and treatment groups.

Conclusion: The results of this study indicated no negative impacts of the vaccine administration during pregnancy on developing of fetuses in rats.

Keywords: COVID-19, Organogenesis, Pregnancy, Rat, SpikoGen, Vaccine

Introduction

Since the human coronaviruses (CoVs) discovery in the 1960s, new CoVs types have emerged and have slowly turned into a threat to public health [1]. At the end of 2019, emergent infections caused by a new CoV were testified in Wuhan, China. The virus was recognized as a novel CoV and formally named coronavirus disease 2019 (COVID-19). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the agent responsible for COVID-19 [2]. Pregnant women are at enhanced risks for severe COVID-19 with greater rates of intensive care, death, and hospitalization in comparison to non-pregnant women [3,4]. However, pregnant women were not included in the initial trials of COVID-19 vaccines, it led to in a lack of data on vaccine-associated profits or adverse effects in this population [5]. Presently, over 30 vaccine types are approved by the U.S. Food and Drug Administration. Among these, six (mumps, Bacillus Calmette–Guérin, rubella, yellow fever, varicella-zoster virus, and rotavirus) are live

vaccines, all of which are contraindicated in pregnant women [6]. Between them, only the anti-rubella vaccine is possibly teratogenic [7]. Still, vaccine strains have low virulence, and there has been no information of fetal malformation after vaccination throughout pregnancy. These vaccines employ conventional technologies, like inactivated and live-attenuated viruses, along with protein subunit vaccines [8,9]. Though, the COVID-19 pandemic urgency has led to a burst of development in messenger RNA (mRNA) and viral vector vaccines. It has been indicated that the possibility of replication of commercially accessible anti-SARS-CoV-2 vaccines such as adenovirus vector or mRNA vaccines in the placenta or the fetus was not probable [10].

While recombinant or inactivated protein vaccines are safe, they typically have poor immunogenicity unless they are made with an appropriate adjuvant [11,12]. Consequently, the application of Advax (GMP-grade Delta-inulin), an anti-inflammatory adjuvant, is supposed to decrease problems of vaccine administration. SpikoGen is made up of Vaxine's unique non-inflammatory Advax and an inoffensive insect cell-based recombinant spike protein of SARS-CoV-2 [13-17]. The SpikoGen vaccine has successfully passed preclinical animal testing and clinical trial phases in Australia (phase 1) and Iran (phase 2 and 3) [18]. Generally, vaccination is done during pregnancy for the following purposes: (1) to protect pregnant women, (2) to protect the fetus from infection inside the uterus, and (3) to protect babies by producing protective levels of maternal antibodies in the newborns after birth. Due to ethical issues and concerns about the vaccine safety for the fetus, in the study of vaccines, pregnant women are considered in special groups and are excluded from the group of volunteers. Therefore, in clinical trial phases 1 through 3, one of the conditions for entering the investigation is that volunteers should not be pregnant or breastfeeding [19]. On the other hand, getting infected with COVID-19 in a pregnant mother is a major concern and creates a big challenge. Considering the potential benefits of vaccine during pregnancy for both mother and infant, and considering the concerns arising from the administration of this vaccine in humans, we assessed the effect of vaccination with SpikoGen during pregnancy on rats' fetal development.

Materials and Methods

Chemical and agents

SpikoGen vaccine was prepared by CinnaGen Company (Tehran, Iran) and was stored at the temperature mentioned by the manufacturer (2–8°C, away from light and moisture). Young adult rats (8 weeks old) were purchased from Razi Institute, Tehran, Iran.

Animals

A total of 105 Wistar rats (50 male and 55 female) weighing between 220–250 g were prepared and housed in an environment that was appropriate for them (light/dark cycle, 6:00 AM–6:00 PM, controlled temperature, 23–25°C), with access to food and water at all times. Prior to the commencement of the experiments, rats were housed in cages apart from one another for a week, which facilitated quicker mating [20]. The reproductive cycle of these rats was monitored, so that on the date of their ovulation, male and female rats were placed in cages with each other for mating for 12 hours. After 12 hours, mating was confirmed through the vaginal plug. The vaginal plug presence was defined as day 0 of pregnancy. All the operative procedures in the experimental procedures, standard husbandry, housing, and handling were accepted via the ethics commission for animal experimentation at the Iran University of Medical Sciences (IR.IUMS.REC.1400.1115).

SpikoGen vaccine preparation

A dose of 25 μg of the vaccine (the same dose used in human) was administered to groups of rats based on the experimental design described in the following section.

Experimental design and grouping

The success of mating was checked via examination of the vaginal plugs. The total number of pregnant rats were 50. The day of vaginal plug diagnosis was considered day 0 of pregnancy. Pregnant rats were caged separately and were casually divided into five groups (N=10). Group 1 (G1): Animals received normal saline before and after pregnancy. Group 2 (G2): Animals received 25 μg/mL of the vaccine 28 days and 14 days before pregnancy. Group 3 (G3): Animals received 25 μg/mL of the vaccine 14 days before pregnancy and 14 days after start of pregnancy. Group 4 (G4): Animals received 25 μg/mL of the vaccine 8 days before pregnancy and 6 days after start of pregnancy. Group 5 (G5): Animals received 25 μg/mL of the vaccine 4 days and 11 days after start of pregnancy (organogenesis period) (Fig. 1) [21].

Body weight, clinical signs, and food consumption were recorded. At the end of the experiments, on the 21st day, pregnant rats were sacrificed using CO_2 and the abdomen was

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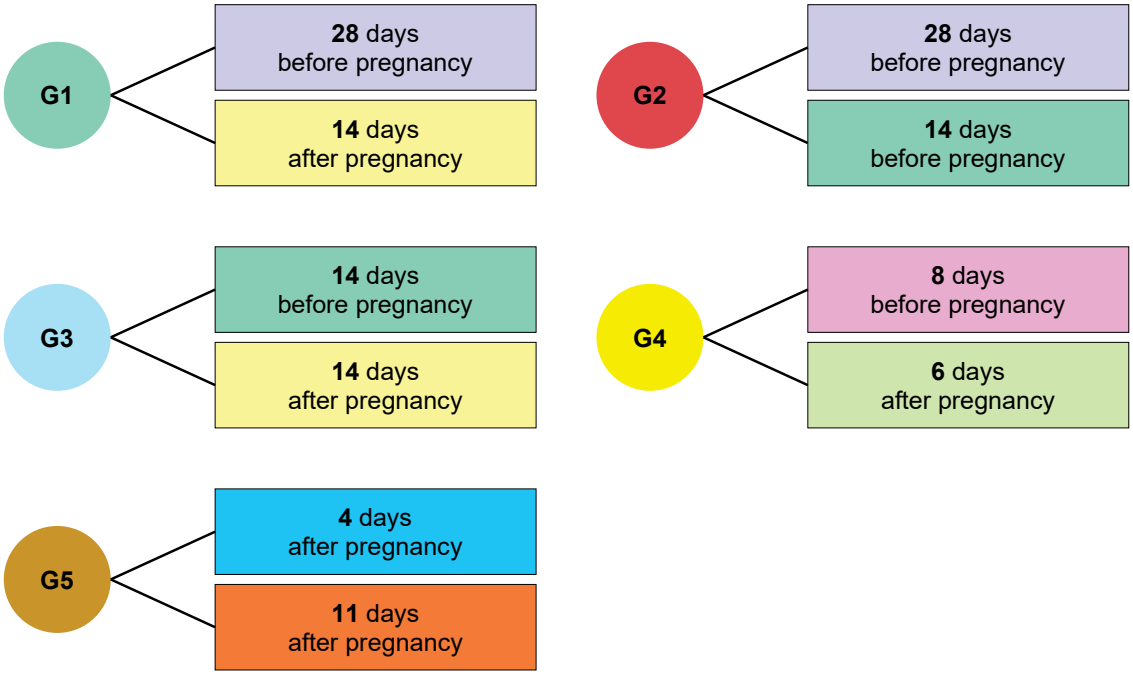

Fig. 1. Treatment timeline in animals before and after pregnancy.

opened by making a 2.5–2 cm incision along the midline. The uterus and fetuses were taken out. Before being placed in a fixative, the fetuses were tested morphologically and cleaned with normal saline. Subsequently, the rat fetuses were kept apart from one another in a box containing 10% formalin for two days in order to solidify and firm up the fetus tissues. After that, the fixing material was switched to a phosphate-buffered saline solution.

Morphological study

The fetuses of treatment groups (N=10) were investigated regarding the number of live and dead fetuses, total number of fetuses, number of abortions, crown-rump length, weight, and height. The fetuses were also evaluated regarding skeletal and morphological anomalies via a stereomicroscope.

Skeletal study

The fetuses of treatment groups (N=10) were located in acetone for 1 day. Next, after removal of the skin the fetuses were positioned in a staining solution containing Alcian Blue, Alizarin Red-S, ethanol, acetic acid, and ethanol. Then, they were stained via microwave radiation. After that, the fetuses were positioned in the solution containing ethanol 95%, KOH 1%, and glycerin for 1 day. Finally, fetuses were investigated regarding probable skeletal and morphological alterations [20].

Radiology study

To determine whether there was a difference in the overall skeletal opacity, radiology imaging of the fetuses (N=6 from each group) was done [22].

Histological study

The fetuses (N=3 from each group) were positioned in paraffin after being fixed in Bouin's solution. After that, the samples endured tissue staining using hematoxylin and eosin (H&E). Next, a light microscope was used to inspect the samples.

Statistical study

Data were analyzed (GraphPad Prism ver. 5.0 graphing and statistics software; GraphPad Software, San Diego, CA, USA) via one-way analysis of variance along with Turkey's multiple comparisons test or Dunnett's test. The t-test was accomplished for number of data analysis. In all the experiments, $p<0.05$ was estimated significant. Data are offered as mean±standard error of the mean (SEM).

Results

Morphological study

The total number of fetuses (dead and alive), weight, number

of abortions, crown-rump length, and the head and tail length were assessed (Table 1).

Impact of Spikogen subunit vaccine on weight of fetuses in treatment groups

There was no considerable difference in the weight of fetuses in treatment groups (G5, G4, G3, and G2) in comparison to the control group (Fig. 2A).

Impact of Spikogen subunit vaccine on the head diameter of fetuses in treatment groups

There was no significant difference ($p>0.05$) in the head diameter of fetuses in treatment groups (G5, G4, G3, and G2) in comparison to the control group (Fig. 2B).

Table 1. Comparison of the number of pregnant rats, the total number of fetuses, the number of dead fetuses, and the number of abortions across different groups

Variable	G1	G2	G3	G4	G5
No. of pregnant rats	10	10	10	10	10
Total no. of fetuses	83	87	85	81	88
No. of dead fetuses	0	1	0	1	1
No. of abortions	0	0	0	0	0

Impact of Spikogen subunit vaccine on tail length of fetuses in treatment groups

There was no considerable difference in the tail length of fetuses in treatment groups (G5, G4, G3, and G2) comparing to the control group (Fig. 2C).

Impact of Spikogen subunit vaccine on the crown-rump length in treatment groups

There was no significant difference in the crown-rump length of the animals in treatment groups (G5, G4, G3, and G2) in comparison to the control group (Fig. 2D).

Radiologic study

The radiology picture confirmed that there was no difference in the overall skeletal opacity and density between control and G2, G3, G4, and G5 groups (Fig. 3).

Histological study

Macroscopic study

Macroscopic examination showed normal anatomic appear-

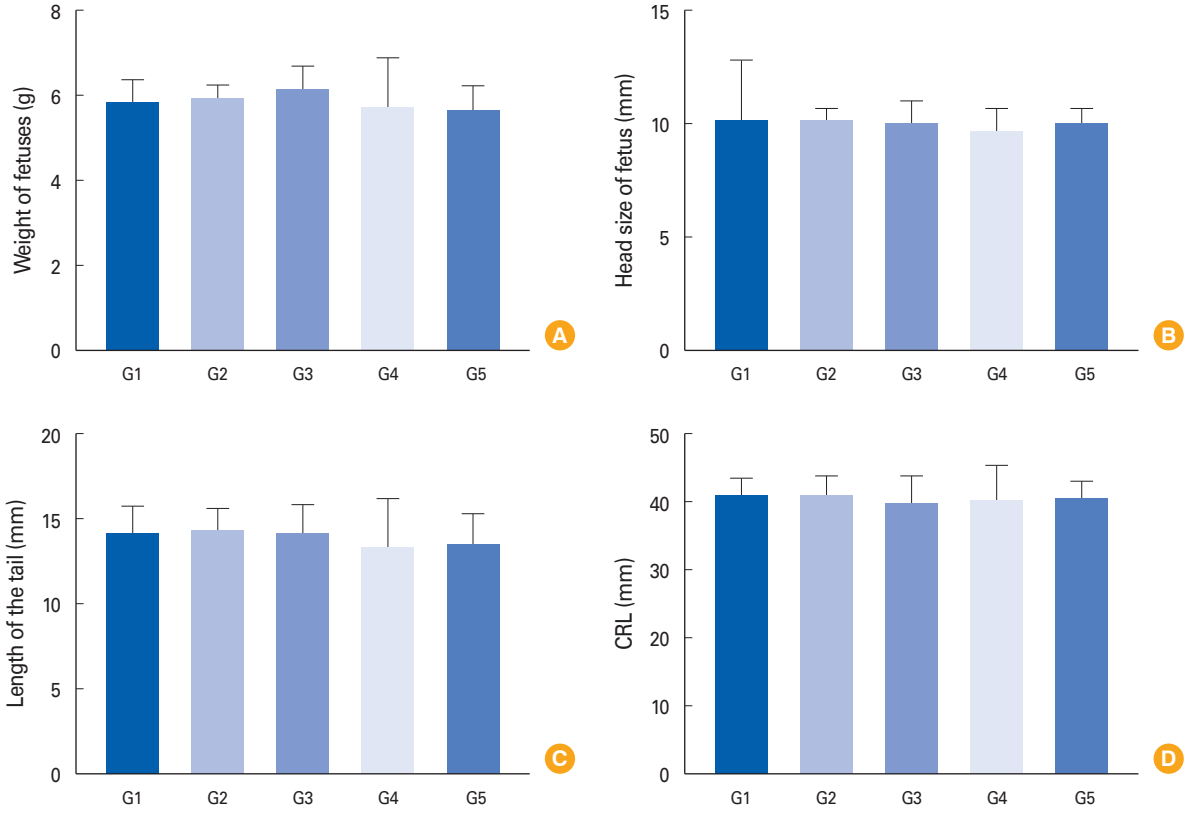

Fig. 2. The effect of the SpikoGen subunit vaccine on the weight of fetuses **(A)**, head size of fetuses (mm) **(B)**, tail length of fetuses **(C)**, and crown-rump length (CRL) of fetuses **(D)** in different groups.

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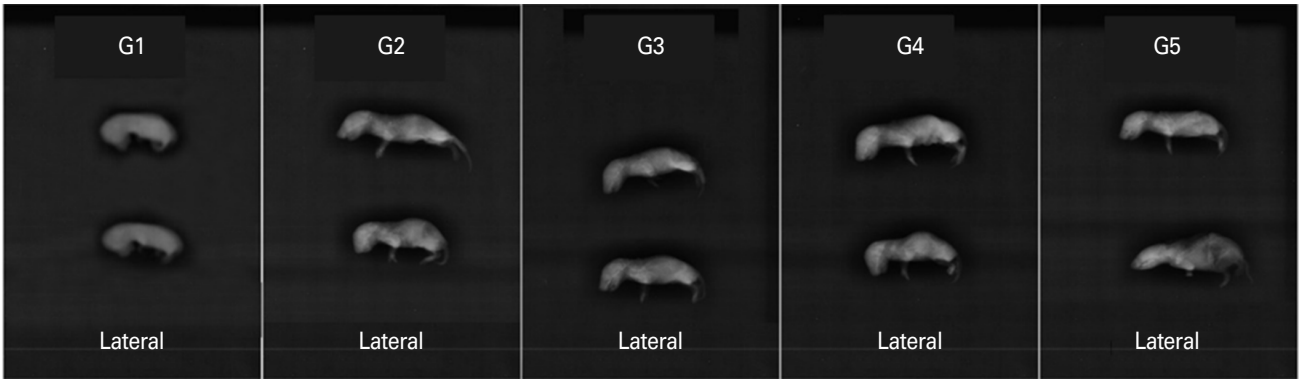

Fig. 3. Radiologic picture of the fetuses in different groups.

Table 2. Macroscopic evaluation of fetuses in different groups

Group	The appearance of the foot	The appearance of the hand	Abnormal appearance
G1	Normal	Normal	Not seen
G2	Normal	Normal	Not seen
G3	Normal	Normal	Not seen
G4	Normal	Normal	Not seen
G5	Normal	Normal	Not seen

ance of the hand and foot in control and treatment groups, including G1, G2, G3, G4, and G5. There was also no abnormal appearance in all fetuses of control and treatment groups (Table 2).

Gross pathology and histopathologic study

Examining the skin, skeleton, and internal organs of the fetuses of rats indicated that there were no congenital malformations, and toes and legs were fully developed. Based on previous investigations [23], all internal organs of the fetuses, including the heart, lung, liver, kidney, and spleen were fully formed and there were no malformations (Fig. 4, Table 3).

Discussion

Pregnancy is one of the risk factors for severe COVID-19. The best approach for decreasing the risk of SARS-CoV-2 infection and limiting its mortality and morbidity is vaccination. Presently, mRNA vaccines are recommended for pregnant women, both by researchers investigating the safety of these vaccines and also by internationally known scientific societies that assess the health status of particular social groups [11,12, 24-26]. Adjuvants induce more durable and greater immune responses and could also be used for imparting a relevant T helper to the immune effector responses [12]. Adjuvants could overcome immune impairments observed with chronic diseases or advancing age. Recombinant vaccines rely on the ability of one or more defined antigens to induce immunity against the pathogen when expressed via plasmids or safe bacterial/viral vectors, or when administered in conjunction with adjuvants. When considering tetanus toxoid or diphtheria vaccines, for instance, recombinant protein vaccines allow the avoidance of some likely concerns raised via vaccines based upon purified macromolecules, such as the risk of co-purification of undesired contaminants or reversal of the toxoids to their toxigenic forms. Another significant issue that this technology resolves is the difficulty in obtaining sufficient amounts of purified antigenic components [25]. Former studies of the SpikoGen have demonstrated robust protection toward SARS-CoV-2 challenge along with the T-cell responses and neutralizing antibodies induction [13-17]. Moreover, results of one study indicated that compared to the other SARS-COV-2 infection-preventing vaccine candidates that have been approved for emergency use, the SpikoGen has led to reduced vaccine administration-related adverse impacts because of the adjuvant with anti-inflammatory properties included in the vaccine formulation. The synthetic viral spike protein elements and adjuvant with anti-inflammatory properties used in vaccine formulation also specified this vaccine as a better applicant regarding tolerability and safety margin [27]. So far, no studies have been conducted on animals and humans during pregnancy. In this study, based on the concerns rising from the COVID-19 vaccine administration in humans, and the possible benefits of this vaccine during pregnancy for both mother and infant, this study evaluated the impact of SpikoGen vaccine on the process of organogenesis during pregnancy. According to the information we have, this

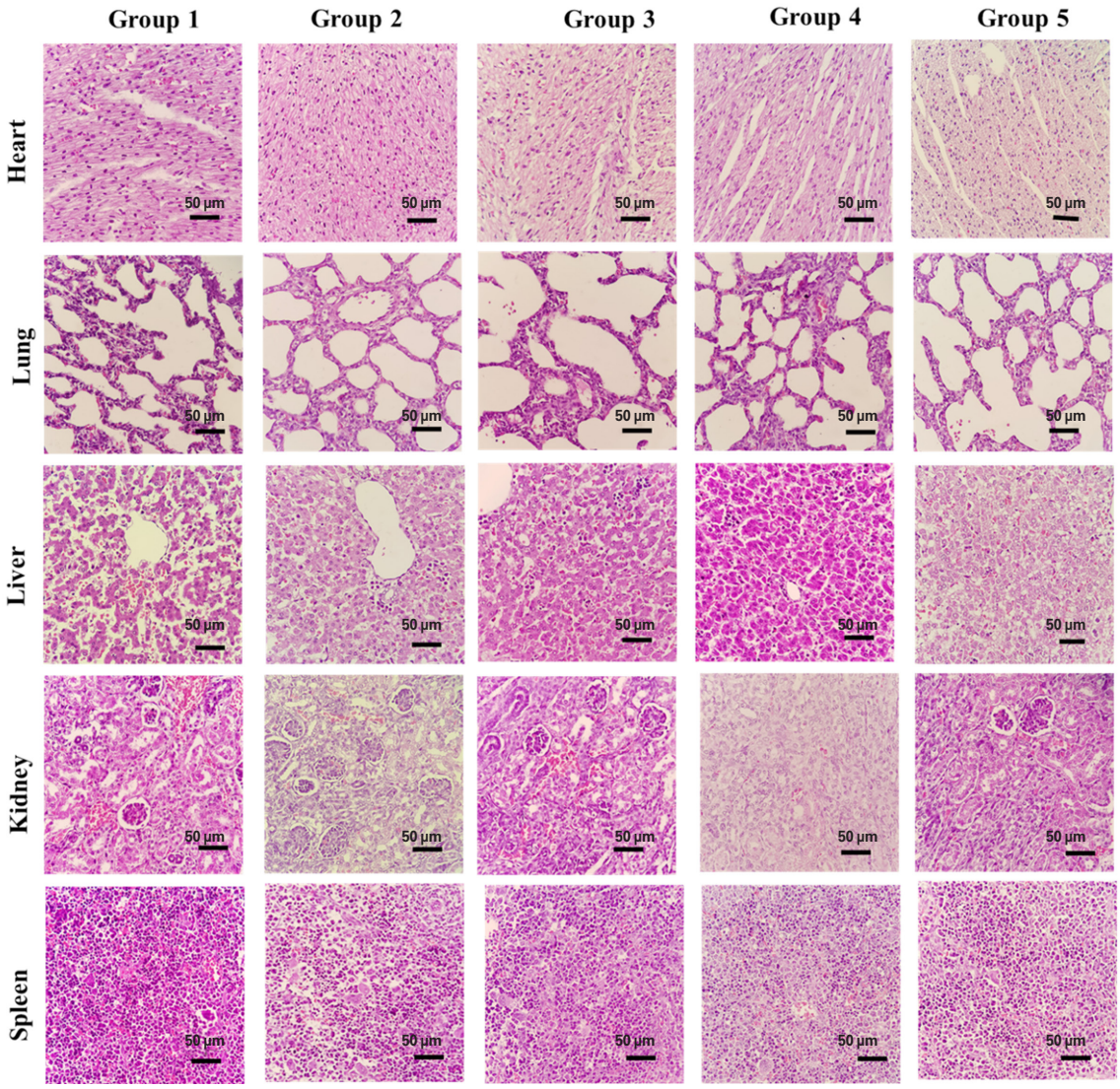

Fig. 4. Histopathologic sections of the heart, lung, liver, kidney, and spleen in experimental groups (H&E stain, ×40; scale bar, 50 μm).

Table 3. Gross evaluation of tissues in fetuses of different groups

Group	Skin[a]	Skeleton[b]	Heart[c]	Lung[d]	Liver[e]	Kidney[f]	Spleen[g]
G1	Absent	Normal configuration of vertebrae in rodents	Absent	Lobation	Lobation	Normal	Normal
G2	Absent	Normal configuration of vertebrae in rodents	Absent	Lobation	Lobation	Normal	Normal
G3	Absent	Normal configuration of vertebrae in rodents	Absent	Lobation	Lobation	Normal	Normal
G4	Absent	Normal configuration of vertebrae in rodents	Absent	Lobation	Lobation	Normal	Normal
G5	Absent	Normal configuration of vertebrae in rodents	Absent	Lobation	Lobation	Normal	Normal

[a]Presence or absence of an accumulation of intersititial fluid in subcutaneous connective tissue, any regional discoloration, extravasated blood beneath the skin, localized region of no skin development, and hernia. [b]Pre-pelvic vertebrae: total=26 (cervical=7, thorax=13, lumbar=6). [c]Acardia and aberration in structure of the heart including in aortic valve, atrial septum, and atrium. [d]Right lobe subdivided into right cranial lobe, right middle lobe, right caudal lobe, and accessory lobe; left lobe subdivided into left medial lobe, and left lateral lobe. [e]Right lobe subdivided into right medial lobe, right lateral lobe, papillary process (cranial and caudal to stomach), and caudate process. [f]Renal discoloration, distension, malposition, and altered texture. [g]Aspleenia, splenomegaly, malposition, split, and misshapen.

was the first study that evaluated the effect of SpikoGen vaccine administration during pregnancy on fetal development in rats. Worldwide, tens of thousands of pregnant people have been immunized against COVID-19 thus far. According to the findings, these vaccinations provided a good degree of protection against severe COVID-19, and there have not been any

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alarming reports of any safety issues. Pregnancy-related data showed that some COVID-19 vaccinations, such as mRNA COVID-19 vaccines, like those from Pfizer/BioNTech (Mainz, Germany) or Moderna (Cambridge, MA, USA), have been well tolerated and may result in high antibody levels being transferred to fetuses [28-30]. In addition, data on the vaccine BNT162b2 indicated that after giving female rats the full human BNT162b2 dose of 30 μg mRNA intramuscularly twice before mating and twice during gestation, there were no effects on the offspring's growth, development, or survival until the end of lactation [21]. In accordance to these studies our results showed that SpikoGen vaccine caused no significant effect on weight, head diameter, tail length, and crown-rump length of the fetuses. Considering the reference in this case [23], our study which was conducted on the skin and skeleton indicated that there were no congenital malformations, and there was no reduction in the number of toes and legs, and all internal organs of the fetus, including the heart, liver, spleen, lungs, kidneys, ribs, vertebral, and sternebrae were fully formed as well and there were no malformations. In addition, radiologic study confirmed that there was no difference in the overall skeletal opacity and density between control and different groups of treatment. Besides, macroscopic analysis revealed that there was no abnormal appearance in all fetuses of treatment groups. The dosage of vaccine consumed in this animal study (25 μg) was the same as the dosage used in humans. We precisely chose this dose to examine whether the SpikoGen vaccine had any possible deleterious impacts on pregnancy. The results of this investigation indicated that vaccination with SpikoGen during pregnancy was not associated with evidence of teratogenicity.

In conclusion, according to the data obtained during this study, SpikoGen subunit vaccine administration in pregnant rats had no adverse effect on fetal development. Therefore, using this vaccine during pregnancy can be safe. It is recommended to conduct more studies on humans to evaluate this vaccine in clinical trial phase.

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