Veterinary Integrative Sciences 2024; 22(3): 933 - 947 DOI; 10.12982/VIS.2024.064

Vet Integr Sci

Veterinary Integrative Sciences

ISSN; 2629-9968 (online)

Website; www.vet.cmu.ac.th/cmvj

Research article

Effect of the biological castration vaccine (Improvac®) on sex hormones and reproductive organs of pigs in Vietnam

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Abstract

The Improvac® vaccine has been shown to improve growth performance, meat quality, and sexual behavior in swine herds in several countries. This study initially investigated the ability of this vaccine to control sex hormones and the development of reproductive organs in Vietnamese crossbred pigs (Yorkshire – Landrace x Duroc). A total of 45 male piglets were randomly divided into three groups: vaccinated at 12 and 18 weeks old, surgically castrated males at 7 days old, and entire males. Meanwhile, 40 female piglets were randomly assigned to one of two groups: those vaccinated at 12 and 16 weeks of age or entire females. Serum from experimental pigs was collected monthly before and after vaccination until slaughter (25 weeks of age). At the time of slaughter, reproductive organs were obtained to assess changes at the macroscopic and microscopic features. Anti-GnRH antibodies in the immunized male and female pigs increased dramatically and remained for several weeks following a booster shot, while serum levels of sex hormones were significantly lower than in the entire group ($P<0.05$). In addition, the reproductive organs of the immunized groups were negatively affected compared to the control groups. The male vaccinated group showed a significant reduction in the size of reproductive organs and irreversible disruption of spermatogenesis and testicular structure. The ovary and reproductive organs in the immunized female group revealed degradation in the size and ovarian follicle development. Taken together, the Improvac® vaccine can decrease sex hormones, thereby disrupting the development of reproductive organs in vaccinated male and female pigs.

Keywords: Biological castration, Improvac®, Pigs, Vietnam

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Article history; *received manuscript: 14 June 2023,*
revised manuscript: 12 January 2024,
accepted manuscript: 20 February 2024,
published online: 18 March 2024
Academic editor: *Korakot Nganvongpanit*

INTRODUCTION

The hypothalamus, a neuroendocrine organ located below the thalamus and above your pituitary gland, is very essential for the regulation of sex hormones in pigs through the secretion of Gonadotropin-Releasing Hormone (GnRH) (Pop et al., 2018). Many factors affect the release of GnRH by the hypothalamus, such as age, weight, nutrient levels, seasons, and environmental temperature (Stratakis and Chrousos, 1997). After being released, GnRH will stimulate the pituitary gland, a gland located just behind the hypothalamus, to secrete Follicle-Stimulating Hormone (FSH) and Luteinizing Hormone (LH) into the bloodstream (Esbenshade et al., 1990). Then, these two hormones follow the blood stream to reach and affect the testicles and ovaries. FSH helps stimulate spermatogenesis and egg production, while LH participates in the main stimulation process for the testes to secrete testosterone and the ovaries to secrete estrogen (Soede et al., 2011). Two hormones, testosterone and estrogen, will follow the blood and reach the organs to promote maturation in pigs.

Understanding the important role of GnRH in the maturation process of pigs, many studies have created vaccines to reduce the concentration of GnRH in the blood, thereby inhibiting or delaying maturation in animals (Cronin et al., 2003; Čandek-Potokar et al., 2017). The Improvac® vaccine serves the same purpose. The essence of the vaccine is a protein containing the epitopes necessary for the production of endogenous anti-GnRH antibodies but not pituitary stimulation. This vaccine can stimulate animals to produce anti-GnRH antibodies, thereby limiting the production of LH/FSH, inhibiting the function of testes and ovaries, and disrupting the maturation process in pigs (Martinez-Giménez et al., 2021). The efficacy of immunocastration has been reported to reduce undesirable sexual behavior in male and female animals (Fàbrega et al., 2010; Rydhmer et al., 2010; Andersson et al., 2012; Quiniou et al., 2012; Brewster and Nevel, 2013; Karaconji et al., 2015). Improvac® vaccination was indicated to improve carcass quality and prevent boar taint in pigs (Fàbrega et al., 2010; Morales et al., 2010; Font-i-Furnols et al., 2012; Xue et al., 2019; Zoels et al., 2020). Besides, the Improvac® vaccine can be used for the contraception of wild animals (Elhay et al., 2007; Botha et al., 2008; Lestari et al., 2018; Martinez-Giménez et al., 2021; Schwarzenberger et al., 2022).

Vietnam is one of the most important pork markets in the world and is the second-biggest pork producer in Asia (Cheung et al., 2023). Therefore, improving the productivity of Vietnamese pig herds is an important process. Since the Improvac® vaccine was reported to be able to improve growth performance and carcass quality in pigs by suppressing the release of sex hormones and the development of reproductive organs, we conducted this study to preliminarily evaluate the efficacy of this vaccine in Vietnamese pig herds. In this study, we only investigated the effects of the vaccine on anti-GnRH antibodies, sex hormones and reproductive organs in a limited number of pigs. However, the results of this study will provide an important basis for us to continue to evaluate the effectiveness of vaccines in improving production productivity and meat quality in large-scale experiments, thereby applying the vaccine to Vietnam's pig industry.

MATERIALS AND METHODS

Ethics approval

The study was conducted in compliance with the institutional rules for the care and use of laboratory animals and using a protocol approved by the Ministry of Agriculture and Rural Development of Vietnam (TCVN 8402:2010).

Animals

This study included 2 separate experiments with 45 male and 40 female crossbred piglets aged 7 days (Yorkshire-Landrace×Duroc). These piglets were carefully selected from 12 litters of healthy sows (Yorkshire-Landrace) that were crossed with Duroc boars of the same origin. The piglets were reared at a commercial farm with a high level of biosecurity. Trial pigs in each group were kept in separate cages but in the same house with temperature controlling by cooling pad, cement floor, 1.2 m^2/pig. All experimental pigs were cared for in the same manner and used commercial complete feed.

Treatment and sampling

Experiment 1 (on male pigs): 45 male piglets were randomly divided into 3 groups, namely immunocastrated males (IM, n=20), surgically castrated males (SM, n=20), and entire males (EM, n=5). IM group was vaccinated with the Improvac® vaccine (2 ml, 200 µg of GnRH-protein conjugate per ml) at 12 and 18 weeks of age. The SM group was surgically castrated at 7 days old. Serums of male pigs were collected at 12, 14, 18, 23, and 25 weeks of age.

Experiment 2 (on female pigs): 40 female piglets were randomly allocated into 2 groups, including those immunized (IF, n=20) with Improvac® vaccine (2 ml) at 12 and 16 weeks of age and entire females (EF, n=20). Serum samples from experimental pigs were collected at 12, 14, 18, 23, and 25 weeks of age. Serums of female pigs were collected at 12, 14, 16, 20, 23, and 25 weeks of age.

All pig groups were kept in separate cages and reared in the same manner. The experimental pigs were slaughtered at 25 weeks of age, and their reproductive organs were collected to evaluate anatomic changes at the macroscopic and microscopic levels.

Serum analysis

Serum from experimental pigs was collected at the indicated times, processed and stored at −20 °C until analyzed. The titer of anti-GnRH antibodies was quantified by Porcine Gonadotropin-Releasing Hormone Antibody Kit (Anti-GnRH) ELISA kit (MyBiosource, USA) with a sensitivity of 0.1 ng/ml. Besides, the concentrations of testosterone and estrogen were evaluated by the Pig Testosterone T ELISA Kit (MyBiosource, USA) and Porcine Estrogen ELISA (MyBioSource, USA), with a sensitivity of <0.05 ng/ml and 5 pg/ml, respectively. Analysis procedures were strictly performed followed under the manufacturer's instructions. The ELISA plates were read at 450 nm in a plate reader (Multiskan FC, Thermo Scientific, USA).

Examination post-mortem

All experimental pigs were weighed at the time of slaughter to minimize stress on the pigs. The macroscopic parameters (length, weight, and diameter) of the reproductive organs in male and female pigs were recorded and evaluated immediately after slaughter. In addition, the tissues of reproductive organs were collected, fixed with 10% formalin, paraffin-embedded, stained H&E, and assessed for histological changes as described in previous studies (Kubale et al., 2013; Mitjana et al., 2020).

Statistical analysis

The data in the study were statistically analyzed using the SPSS 25 software (IBM - International Business Machines, USA). Initially, the data was determined by the distribution of the data by using the Shapiro-Wilk method. If the normal distribution was followed, the data was further analyzed by the one-way ANOVA and Tukey methods. The opposite was analyzed by Kruskal-Wallis and Man-Whitney. The difference between groups was significant with $P<0.05$.

RESULTS

Experiment 1 (on male pigs)

Serum analysis

Anti-GnRH antibody levels in the IM group increased slightly after the first injection (6 and 8 weeks post-vaccination), then dramatically increased after the booster shot at 23 and 25 weeks of age (>0.4 ng/ml; Figure 1). The amounts of these antibodies in the EM and SM groups were significantly lower than that of the IM group after the second vaccination and remained at about 0.3 ng/ml during the experiment. In addition, in the IM group, testosterone levels decreased significantly after the 2nd dose of vaccination, which was no different from the SM group. Meanwhile, the EM pig group witnessed an increase in serum testosterone levels at 23 and 25 weeks of age, which was significantly greater than the IM and SM groups ($P<0.001$).

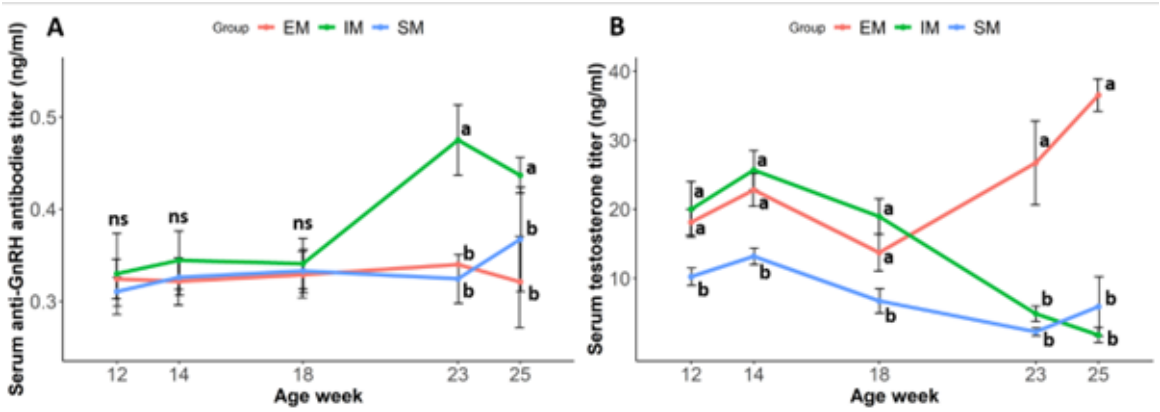

Figure 1 Levels of anti-GnRH antibodies (A) and testosterone (B) in male groups. Different letters (a and b) indicate statistically significant differences (P<0.05) among the groups; ns: no statistical difference.

Reproductive organs

For the macroscopic parameters at the time of slaughter, the experimental pigs did not exhibit statistically significant differences in live weights ($P>0.05$). Although there was no difference in the parameters of the penis ($P>0.05$), the testicles and accessory gonads of the IM group were significantly smaller and lighter in size and weight compared with the EM group ($P<0.05$; Table 1). Besides, the weights and sizes of penis and cowper gland in the SM group were still significantly smaller than the other two groups ($P<0.05$).

For the microscopic parameters in the IM group, the seminiferous tubules mostly degenerated with a size reduction of tubular walls compared with the EM group ($P<0.001$; Table 2). There was almost no growth of spermatocytes in seminiferous tubule lumens, so only about 20% of pigs in the IM group had spermatozoa in the lumen compared to 100% of the EM group. In addition, only 80% of IM pigs had primary and secondary spermatocytes, while all EM pigs had these cells. The Leydig cells in the IM group showed cytoplasmic degeneration, and the nucleus shrank with abnormal morphology. Degeneration was also observed in the epididymis of the IM group, with a significant reduction in lumen area compared with the EM group ($P<0.001$; Figure 2B,C). These tubules were also found to be thin due to fibrosification of the muscle layers. This could make the height of tubule walls in the IM group significantly thicker than that of the SM group ($P<0.001$). 80% of pigs in the IM group did not have sperm in the lumen of the epididymis, but the rest contained very little sperm, with most being abnormal sperm. The male accessory reproductive glands of the IM group also showed fibrosis and a marked reduction in the number of cells and in the area of the exocrine ducts compared with the EM group ($P<0.001$).

Table 1 Effect of Improvac® vaccine on male reproductive organs at macroscopic levels

Parameters	EM group	IM group	SM group	*P*-value
Live weight at slaughter (kg)	99.60±5.90	104.38±1.96	104.11±1.83	>0.05
Penis length (mm)	485.82±31.59	525.99±14.68	450.89±16.98	<0.05
Penis weight (g)	91.32±15.08	65.10±5.09	56.20±5.27	<0.05
Penis perimeter (mm)	44.40±4.27	41.33±1.54	34.00±1.31	<0.05
Bulbourethral gland weight (g)	76.93±8.83	22.60±3.38	3.29±0.38	<0.001
Bulbourethral gland length (mm)	132.80±9.27	82.95±3.22	60.33±4.59	<0.001
Testis weight (g)	231.00±20.57	93.03±11.59	-	<0.001
Testicular horizontal circumference (mm)	19.58±0.93	13.81±0.51	-	<0.001
Testicular vertical circumference (mm)	254.30±11.59	189.67±7.45	-	<0.001
Testicular small cross-sectioned diameter (mm)	61.80±3.34	44.64±2.09	-	<0.001
Testicular large cross-sectioned diameter (mm)	66.60±2.94	50.40±2.90	-	<0.05
Testicular small longitudinal-sectioned diameter (mm)	69.40±3.75	48.95±2.01	-	<0.001
Testicular large longitudinal-sectioned diameter (mm)	105.60±2.34	75.19±3.72	-	<0.001
Epididymis weight (g)	64.30±7.09	30.73±2.37	-	<0.001
Epididymis length (mm)	245.90±19.85	176.75±6.91	-	<0.001

Table 2 Effect of Improvac® vaccine on male reproductive organs at microscopic levels

Parameters	EM group	IM group	*P*-value
Area of seminiferous tubules (μm^2)	30.59±3.11	12.82±1.16	<0.001
Height of seminiferous tubule epithelium (μm)	965.03±78.95	280.28±11.51	<0.001
Area of bulbourethral gland (μm^2)	151.53±17.84	21.48±1.38	<0.001
Area of epididymis tubules (μm^2)	3182.91±221.73	1912.91±111.34	<0.001
Area of epididymis lumen (μm^2)	1596.29±180.75	767.67±96.89	<0.001
Height of epididymis tubule epithelium (μm)	7.85±0.60	6.39±0.36	<0.05
Height of epididymis tubule muscle (μm)	1.84±0.11	3.15±0.19	<0.001

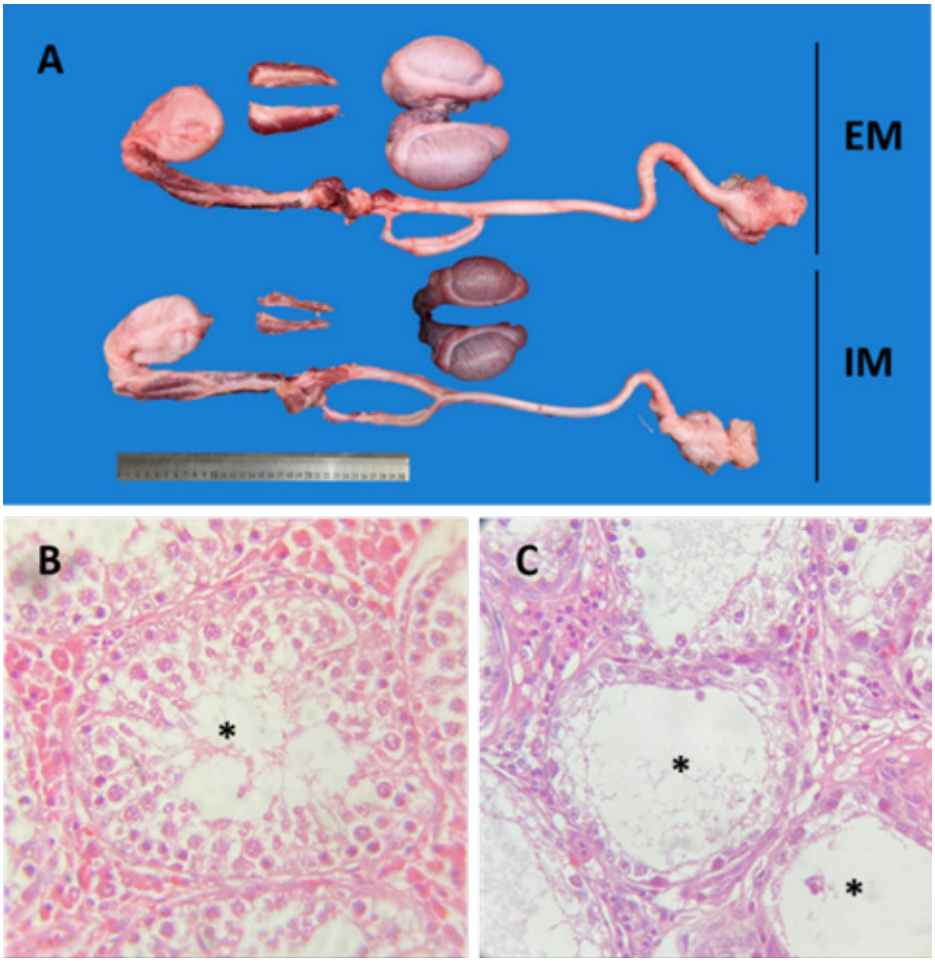

Figure 2 The size of testicles and accessory gonads of EM and IM groups (A), bar 30 cm. Seminiferous tubule histology (asterisk) in EM group (B) and IM group (C), H&E 40X.

Experiment 2 (on female pigs)

Serum analysis

The concentration of anti-GnRH antibodies in the IF group increased slightly and was significantly higher than that of the EF group at week 16 of age (P<0.05). After the second injection, the amount of these antibodies in the IF group increased and remained unchanged in the following weeks (Figure 3). At 25 weeks of age, the anti-GnRH antibody titer of the IF group was 0.66±0.11 ng/ml, which was significantly greater than that of the EF group with 0.37±0.03 ng/ml (P<0.05). Besides, the estrogen concentration in the IF group was always low and maintained until the end of the experiment (about 40 pg/ml). Meanwhile, the amount of serum estrogen in the EF group continuously increased and was significantly higher than that in the IF group at the time points after the booster shot (P<0.05). These results suggest that the increase in anti-GnRH antibodies after the second vaccination had an inhibitory effect on sex hormone production in experimental pigs.

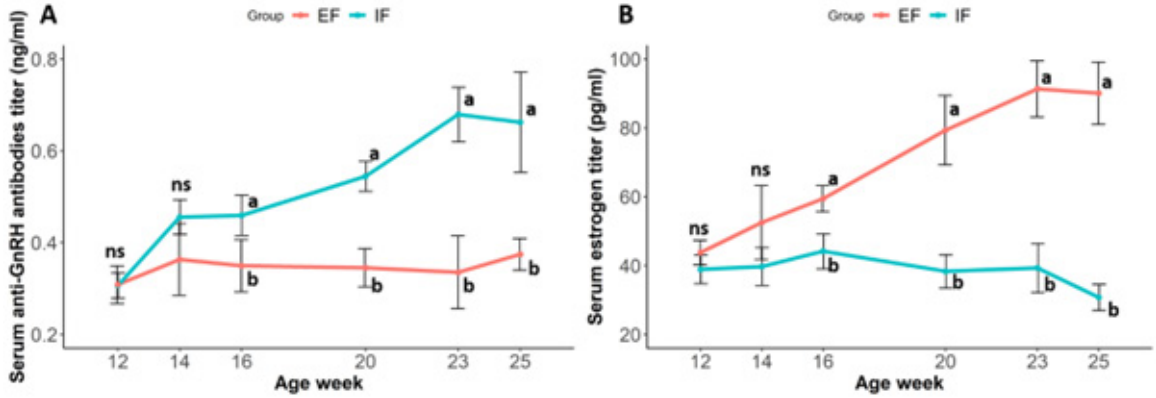

Figure 3 Levels of anti-GnRH antibodies (A) and estrogen (B) in female groups. Different letters (a and b) indicate significant differences (P<0.05) among the groups; ns: no statistical difference.

Reproductive organs

For the macroscopic parameters, the weight and length of female reproductive organs in the IF group were mostly significantly lower than in the EF group (Table 3). No follicles were found on the ovaries of vaccination pigs, while almost mature follicles were exhibited on those of control pigs (Figure 4A). This result showed that the vaccine has an inhibitory effect on the development of female reproductive organs. Besides, we identified that there is a positive correlation between estrogen levels and the parameters of reproductive organs. This showed that estrogen played a role in the development of the reproductive organs, affecting the size and weight of the reproductive organs as well as the ovaries.

In the microscopic parameters, the number of follicle types in a 40X microfield was significantly higher in the IF group than in the EF group (P< 0.05; Table 4). However, the size of the follicles in the EF group was larger than that of the IF group (Figure 4B,C). Therefore, we will not compare the number of follicles between the two groups but compare the presence rates of different types of follicles in the same group. Although the prevalence of secondary follicles was significantly higher in the IF group than in the EF group (P<0.05), the proportions of Graafian follicles and corpus luteum in the EF group were

greater than in the IF group (P<0.05) (Table 4). This difference may be due to the low estrogen levels in the serum of immunized pigs. In the IF group, serum estrogen levels were consistently low, so the secondary follicles probably tended to be degraded instead of growing into Graafian follicles. Therefore, the rate of atretic follicles (degraded follicles) in the IF group was significantly higher than that of the EF group (P<0.01). 85.7% of pigs in the EF group had corpus luteum, while the IF group did not record any appearances of corpus luteum. The corpus luteum was not observed in the IF group; instead, the presence of degenerating follicles indicated the disruption of the follicular growth, which would presumably affect the normal estrus ability of vaccinated pigs

Table 3 Effect of Improvac® vaccine on female reproductive organs at macroscopic levels

Parameters	EF group	IF group	*P*-value
Live weight at slaughter (kg)	99.0±1.9	100.0±2.4	>0.05
Total reproductive system weight (g)	187.0±13.5	93.5±5.1	<0.01
Vagina length (mm)	213.0±14.0	165.2±7.5	<0.01
Uterine length (mm)	356.0±29.2	232.2±17.2	<0.05
Vagina circumference (mm)	57.1±2.7	47.2±5.2	>0.05
Uterine circumference (mm)	37.9±2.0	30.2±1.4	<0.05
Uterine horn circumference (mm)	33.1±2.5	23.3±1.4	<0.01
Ovary weight (g)	3.2±0.2	1.0±0.1	<0.001

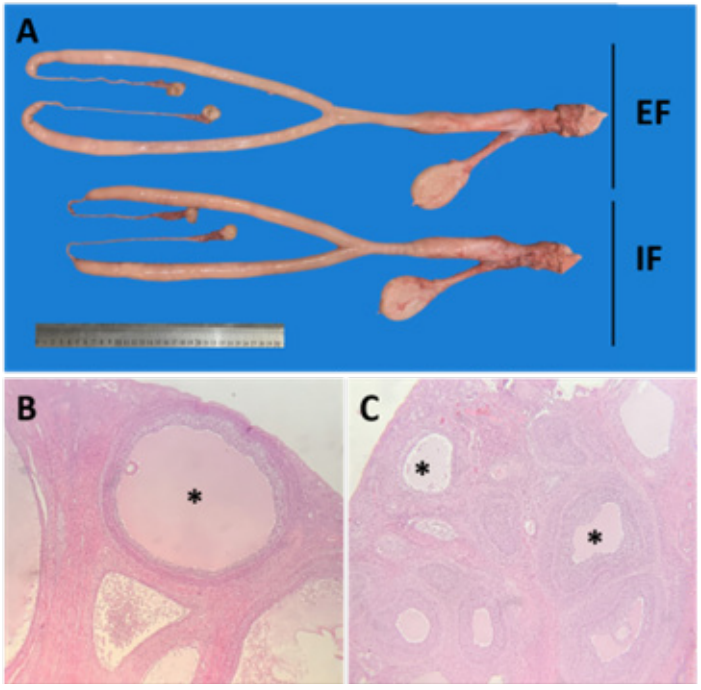

Figure 4 The size of reproductive organs of EF and IF groups (A), bar 30 cm. Ovarian histology (follicles: asterisk) in EF group (B) and IF group (C), H&E 10X.

Table 4 Percentage of follicle types on female ovaries

Parameters	Numbers			Percentages		
	EF group	IF group	p-value	EF group	IF group	*P*-value
Secondary follicles	8.58±1.96	20.72±4.13	<0.05	21.41	27.50	<0.05
Graafian follicles	19.25±2.35	31.36±4.60	<0.05	48.02	41.62	<0.05
Atretic follicles	9.33±1.72	22.82±5.53	<0.05	23.28	30.27	<0.01
Corpus luteum	2.92±0.67	0.45±0.45	<0.01	7.27	0.60	<0.001

DISCUSSION

Experiment 1 (on male pigs)

In this study, we could not find any obvious effects of the Improvac® vaccine after the first immunization, which was in line with the study of Claus et al. (2007). However, in the study of Zamaratskaia et al. (2008), anti-GnRH antibody titers of immunized pigs even increased and were significantly higher than those of entire and surgically castrated pigs after the first vaccine dose. This is probably due to the use of more aggressive adjuvants (Claus et al., 2007). Besides, anti-GnRH antibodies only developed rapidly after a booster shot, which is in agreement with previous studies (Zamaratskaia et al., 2008; Brunius et al., 2011). After the second vaccination, the titers of anti-GnRH antibodies of vaccinated pigs increased quickly and then steadily reduced, but they were still significantly higher than those of entire male pigs (Brunius et al., 2011). This result was similar to the Bopriva vaccine in pubertal bulls (Janett et al., 2012). In addition, the concentration of testosterone in the IM group decreased rapidly to that of the SM group after the booster shot, which is consistent with previous studies (Brunius et al., 2011; Vázquez et al., 2020). The second vaccination was also found to interrupt the rise of testosterone in vaccinated pigs after 2 and 5 weeks (Kubale et al., 2013). On the day before slaughter, testosterone concentrations of vaccinated pigs were significantly lower than those of control pigs (Einarsson et al., 2011). Testosterone levels in vaccinated pigs were even undetectable at slaughter (Zamaratskaia et al., 2008). Testosterone levels in the cows and elephants vaccinated against GnRH were also significantly lower than those of the unvaccinated group after the second vaccination (Janett et al., 2012; Lueders et al., 2014). Taken together, the vaccine can stimulate a strong immune response against endogenous GnRH within 2 weeks after a booster shot, which leads to low levels of GnRH in immunized pigs. As a consequence, the hypothalamic-pituitary-gonadal axis is interrupted, and the secretion of FSH and LH is significantly reduced, and thus sex hormones are not released.

In the present study, we found that vaccinated pigs had lower weight as well as length of testes and male accessory reproductive glands than entire male pigs. Similarly, vaccinated pigs had significant reductions in both testes weight and bulbourethral gland length compared with controls (Zamaratskaia et al., 2008; Einarsson et al., 2009; Gispert et al., 2010; Morales et al., 2010; Einarsson et al., 2011). Accessory sex glands can be used as a tool to evaluate the efficacy of immunocastration in male pigs (Bonneau, 2010). Therefore, the reduction in size of reproductive organs, especially accessory reproductive glands, revealed that the Improvac® vaccine can interrupt the maturation of vaccinated pigs (Kubale et al., 2013). Moreover, the testicular histological

status was clearly affected by vaccination. Spermatogenesis was also clearly disrupted in immunized pigs with the degeneration of seminiferous tubules and almost no spermatogenesis in tubular cells, as stated earlier (Earl et al., 2006; Ülker et al., 2009; Einarsson et al., 2009; Mitjana et al., 2020). 80% of vaccinated pigs had both primary and secondary spermatocytes, but only 20% of pigs had sperm in the tubule. The abnormal morphology and degeneration of Leydig cells can be the cause of the decrease in serum testosterone concentration (Einarsson et al., 2011; Kubale et al., 2013). In fact, testosterone is an essential hormone for spermatogenesis and germ cells (Sofikitis et al., 2008). Taken together, these results showed that because the Improvac® vaccine affected the number and size of the Leydig cells, the testosterone titers dropped in vaccinated pigs, which led to irreversible disruption of spermatogenesis and testicular structure. Furthermore, a small proportion of vaccinated pigs also found sperm in the tubules. This showed that although the Improvac® vaccine had a marked inhibitory effect on the development of the male sex organs, it was not as completely inhibited as surgical castration (Brunius et al., 2011; Kubale et al., 2013; Zoels et al., 2020).

Experiment 2 (on female pigs)

In the present study, anti-GnRH antibody levels of vaccinated female pigs slightly increased after the first vaccination and dramatically rose 2 weeks after the second injection. This was similar to the finding of Dalmau et al. (2015) that more than 3 weeks after the second injection, crossbred Iberian female pigs exhibited elevated levels of anti-GnRH antibodies and low levels of progesterone. Besides, the sexual hormone titers (estrogen) of the vaccinated pigs in the study remained unchanged throughout the experimental period. This was in line with progesterone hormones in previous studies. The progesterone concentration started to be significantly different between vaccinated and control pigs around 10 days after the second vaccination (Dalmau et al., 2015). Besides, the progesterone titers in vaccinated female pigs were significantly lower than control pigs from 4 weeks after the booster shot onwards (Hernández-García et al., 2013). The low levels of progesterone in vaccinated pigs showed that vaccinated gilts did not reach puberty until the end of the experiment (46 weeks). The circulating progesterone titers of vaccinated Chinese SuHai pigs were significantly lower than those of controls 1 day before slaughtering (Xue et al., 2019). These findings were in line with those in the male experiment, which showed that the Improvac® vaccine seems to inhibit the sexual hormones several days after a booster shot.

In addition, the reproductive organs of vaccinated female pigs were clearly affected by vaccination, with lower weight and length than entire pigs. The reproductive organs of vaccinated pigs were in a pre-pubertal and infantile state at slaughter (Hernández-García et al., 2013). At slaughter, the weights of the ovary and reproductive glands were also found to decrease by Improvac® vaccination (Oliver et al., 2003; Mitjana et al., 2020). Similarly, the mean weight of ovarian and uterine horns in vaccinated pigs was significantly lower than that of controls (Hernández-García et al., 2013; Dalmau et al., 2015; Xue et al., 2019). Besides, almost no follicles can be observed on any of the ovaries of the vaccinated group in this study, which was in agreement with the findings in Chinese SuHuai pigs (Xue et al., 2019). A previous study showed that no follicles were observed on the ovaries while follicles were present in all pigs in

the control group (Dalmau et al., 2015). On the ovaries of vaccinated gilts, all follicles seem to be immature, small, and invisible (Hernández-García et al., 2013). The contraceptive efficacy of Improvac® vaccine was reported in both female giraffes, mares, and beef calves (Elhay et al., 2007; Lestari et al., 2018; Schütz et al., 2021; Schwarzenberger et al., 2022). These results indicated that the Improvac® vaccine successfully suppressed the development of female reproductive organs in vaccinated animals.

CONCLUSIONS

Improvac® vaccine can stimulate experimental pigs (male and female) to produce high and prolonged anti-GnRH antibodies, especially after a booster shot. This has significantly reduced the concentration of the sex hormones (testosterone in males and estrogen in female pigs), thereby inhibiting the development of male and female reproductive organs at both the macroscopic and microscopic levels.

AUTHOR CONTRIBUTIONS

Danh Cong Lai, Nam Minh Nguyen, Duy Tien Do: Conceptualization and design the experiment, investigation, supervision, editing and finalization.
Khanh Tran Doan Vinh, Hue Vo Thi, Phong Du Dai: Investigation, methodology, formal analysis, manuscript preparation.

CONFLICT OF INTEREST

We have no conflict of interest.

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How to cite this article;

Danh Cong Lai, Nam Minh Nguyen, Khanh Tran Doan Vinh, Hue Vo Thi, Phong Du Dai and Duy Tien Do. Effect of the biological castration vaccine (Improvac®) on sex hormones and reproductive organs of pigs in Vietnam. Veterinary Integrative Sciences. 2024; 22(3): 933 - 947