Prevalence of congenital malformation among neonates born after the use of progesterone for luteal support during IVF and ICSI cycles

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Abstract—**Introduction: This study assessed the prevalence of congenital malformation among neonates born after using progesterone for luteal support in patients undergoing IVF and ICSI cycles.**

Methods: This retrospective cohort study was conducted in the Reproductive Endocrinology and Infertility Department of a tertiary hospital. Two groups were compared: one group received only Cyclogest or Crinone gel, and the other group received a combination of Cyclogest or Crinone gel with Proluton Depot injection

Results: A total of 91 patients were included, all of whom took progesterone during their IVF and ICSI cycles. The minimum age of the participants was 21, and the maximum was 41. 16.5% (n=15) patients who received progesterone for luteal support during their IVF and ICSI cycles gave birth to infants with congenital malformation, while 76 (83.5%) did not. The most commonly observed congenital malformation was patent ductus arteriosus, observed in 5 cases (5.49%), followed by delayed speech observed in 2 (2.2%). Brachydactyly, Down syndrome, autism spectrum disorder, and a number of other conditions were observed at a rate of 1.1%. Ultimately, no significant association was found between the two groups and the incidence of congenital malformations (p = 0.121).

Conclusion: Our review indicates that the incidence of congenital anomalies was similar across the different treatment groups.

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Index Terms—**Congenital Abnormalities, Fertilization in Vitro, Progesterone, Sperm Injections Intracytoplasmic.**

I. Introduction

Progesterone is a hormone naturally produced by the corpus luteum post-ovulation. It is responsible for endometrial priming during the secretory phase of the preimplantation period, by which time the endometrium has been exposed to oestrogen during the proliferative phase of the cycle [1]. Progesterone is essential for the support of the implanted fertilised ovum and for maintaining pregnancy. A synthetic form of this hormone, known as progestins, is widely available with multiple routes of administration, including intramuscular, oral, rectal and vaginal [2]. Progestins are used for endometrial support during the ovulation induction cycle, in vitro fertilisation cycle, and in cases with proven luteal phase defect [3]. Intramuscular progesterone is considered the best in terms of rapid absorption and has a much longer half-life and therapeutic effect compared with other routes. However, it is only available in a handful of countries, and has the undesired side effect of pain at the injection site [4]. Several etiological factors influence the decision to induce ovulation, including female subfertility conditions such as polycystic ovarian syndrome and endometriosis. It is also worth mentioning the empirical use of progestogens [5].

Multiple gestations carry greater risk of congenital malformation than singletons [6], with genital masculinisation of the female foetus and hypospadias in the male foetus among the well-studied anomalies [7]. Other non-genital birth defects include spina bifida, cleft lip, congenital heart defects, oesophageal

fistula, intestinal anomalies, umbilical hernia, DiGeorge's syndrome, and limb defects including polyductely [8].

Although progesterone can inhibit myometrial contraction in vitro, progesterone levels are high during pregnancy and there is no evidence that women who deliver preterm have lower progesterone levels. While vaginal progesterone is not approved for the prevention of preterm birth, it has been widely used by physicians around the world for this purpose, and is endorsed by expert guideline groups [9].

It is interesting to note that our review of studies on progesterone and congenital malformation worldwide yielded conflicting results. For instance, prenatal progesterone exposure in the second and third trimester does not seem to have long-term effects after a follow-up at 48 or 60 weeks of age [6]. On the other hand, the use of progesterone soft capsules (Utrogestan) in short-protocol patients receiving in vitro fertilisation with frozen-thawed embryo transfer revealed neonatal defects of less than 1% [10].

Animal studies of maternal progesterone administration revealed a greater increase in progesterone concentration in males than in females. This suggests the possibility of foetal sex-related effects from the use of progesterone during early pregnancy [11]. Such administration in other animal models caused sclerosis, narrowing and shortening of the forelimb skeleton, shortening and fusion of the hindlimb, and shortening of the skeleton, and leukemia cutis of the forelimb. Among the previously mentioned deformities, those of the hindlimb are the most common. The histopathology of foetuses treated with low progesterone showed seminiferous tubule degeneration, while those treated with high progesterone showed haemorrhage between the seminiferous tubules and congested blood vessels. Samples treated with a low concentration of progesterone showed incomplete development of the sex cords with mild degeneration, in contrast to those receiving high concentrations, which showed atrophy of the sex cord and poorly developed ovaries [12].

Recently, the Triple P trial showed that children born from mothers with a short cervix (≤ 30 mm) exposed to vaginal progesterone did not differ from others with regard to neurodevelopmental, health-related, behavioral, and physical outcomes [13]. Nonetheless, regional studies are lacking. This study aims to assess the prevalence of congenital malformation among neonates born after the use of progesterone for luteal support in patients undergoing IVF and ICSI cycles in Saudi Arabia.

II. Methodology

This retrospective cohort study was conducted in the Reproductive Endocrinology and Infertility Department of a tertiary hospital, from January 2022 to January 2023. Included were all women who had undergone IVF and ICSI and had received luteal support in the form of vaginal progesterone or who had received both vaginal progesterone (Cyclogest) and intramuscular progesterone (Proluton) from the Reproductive Endocrinology and Infertility Department between January 2017 and June 2018, with a comparison between the groups for the prevalence of congenital neonatal malformations. Data were collected by calling each patient and asking them the survey questions after obtaining their consent.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) Version 23. Frequency and percentages were used to display categorical variables, while minimum, maximum, mean, and standard deviation were used to present numerical variables. Independent t-test and chi-square tests were applied to test for association, and a significance level of 0.05 was selected.

Ethical approval was obtained from King Fahd Medical City, with IRB #22-99E.

III. Results

Demographics:

Out of 168 patients who met the inclusion criteria, a total of 91 were included in this study, signifying a response rate of 54%. Some patients refused to participate, while others were excluded due to clerical errors such as missing patient data or incorrect telephone numbers. The socio-demographic and academic profiles of the participants were collected; the minimum age was 21 years, the maximum age was 41, and the mean was 31.19 (+ 4.02) years. As for BMI, the minimum was 17.3, the maximum was 37.5, and the mean was 27.27 + 4.55 kg/m2.

Type of progesterone used:

45 (49.5%) patients received Cyclogest (vaginal progesterone), 30 (33%) received Crinone gel, 11 (12.1%) received both Cyclogest and Proluton Depot injection, while 5 (5.5%) received both Crinone gel and Proluton Depot injection. Figure 1 illustrates the type of progesterone used for luteal support.

Congenital malformation:

Figure 2 demonstrates the incidence rate of congenital malformation after the use of progesterone for luteal support. 15 (16.5%) patients who received progesterone during their IVF and ICSI cycles gave birth to babies with congenital malformation, while 76 (83.5%) did not. Table 1 illustrates the congenital malformation that was observed. The most commonly congenital malformation was patent ductus arteriosus observed in 5 (5.49%), followed by delay in speech observed in 2 (2.2%). Table 2 displays the comparison of congenital malformation incidence across the type of progesterone given for luteal support. No significant association was found ($p = 0.121$). Likewise, there was no significant association found between the incidence of congenital malformation and either age or BMI; $t(88)= 0.152$, $p = 0.88$, $t(89) = 0.123$, $p = 0.90$; respectively.

IV. Discussion

This retrospective cohort study evaluated the prevalence of congenital malformation among neonates born after the use of progesterone for luteal support in patients undergoing IVF and ICSI cycles. No significant association was found in this study between the incidence of congenital malformation and maternal age or BMI. This finding is similar to that of another prospective cohort study which also showed no association with BMI or age. Likewise, a recent randomised clinical trial, published in 2022, showed a similar result. The use of luteal phase support resulted in high patient satisfaction and a great pregnancy outcome [14].

In our study, the most commonly noted congenital malformation was patent ductus arteriosus, which was observed in 5 cases (5.49%), followed by delayed speech, observed in 2 (2.2%). Brachydactyly, Down syndrome, autism spectrum disorder, and a number of other conditions were observed at a rate of (1.1%). This small number of congenital malformations indicates a minimal association between congenital malformation and the use of progesterone.

A large retrospective cohort study enrolled a total of 16,493 infants from IVF and FET cycles after treatment with either progestin-primed ovarian stimulation (n = 15,245) or gonadotropin-releasing hormone antagonist (n = 1,248). The most common congenital malformations were circulatory system malformations, followed by those of the musculoskeletal system, digestive system, and eye, ear, face, and neck [15].

Another retrospective cohort study revealed that the most common congenital malformation was of the circulatory system, followed by cleft lip and cleft palate, urinary system malformations, and musculoskeletal system malformations [16]. A study including 3,556 live-born infants showed that the main type of malformation, after in-vitro fertilisation and vitrified embryo transfer cycles using dydrogesterone as an alternative progestin in the progestin-primed ovarian stimulation (PPOS) protocol, is of the circulatory system, most commonly atrial septal defect and atrioventricular septal defect, followed by digestive system malformations [3]. On the other hand, a previous study demonstrated no significantly elevated rate of congenital anomalies in infants after treatment with luteal-phase ovarian stimulation (LPS) compared with the conventional ovarian stimulation protocol [17].

It is also important to examine the incidence of congenital malformations in relation to each type of progesterone used for luteal support, since each one is administered differently. It was thought that the route of administration might contribute to congenital malformation; however, no significant association was found between the type of progesterone used and congenital malformation, ($p=0.121$). A recent study, conducted in 2017 to establish the efficacy of Gestone and Cyclogest for luteal phase support in IVF cycles, had similar results to our findings [3]. A retrospective cohort study found that the administration of dydrogesterone was a safe option and there was no increase in congenital malformation [16].

Another study done on the efficacy of progesterone gel combined with oral dydrogesterone showed no significant association between their use and congenital malformation [18].

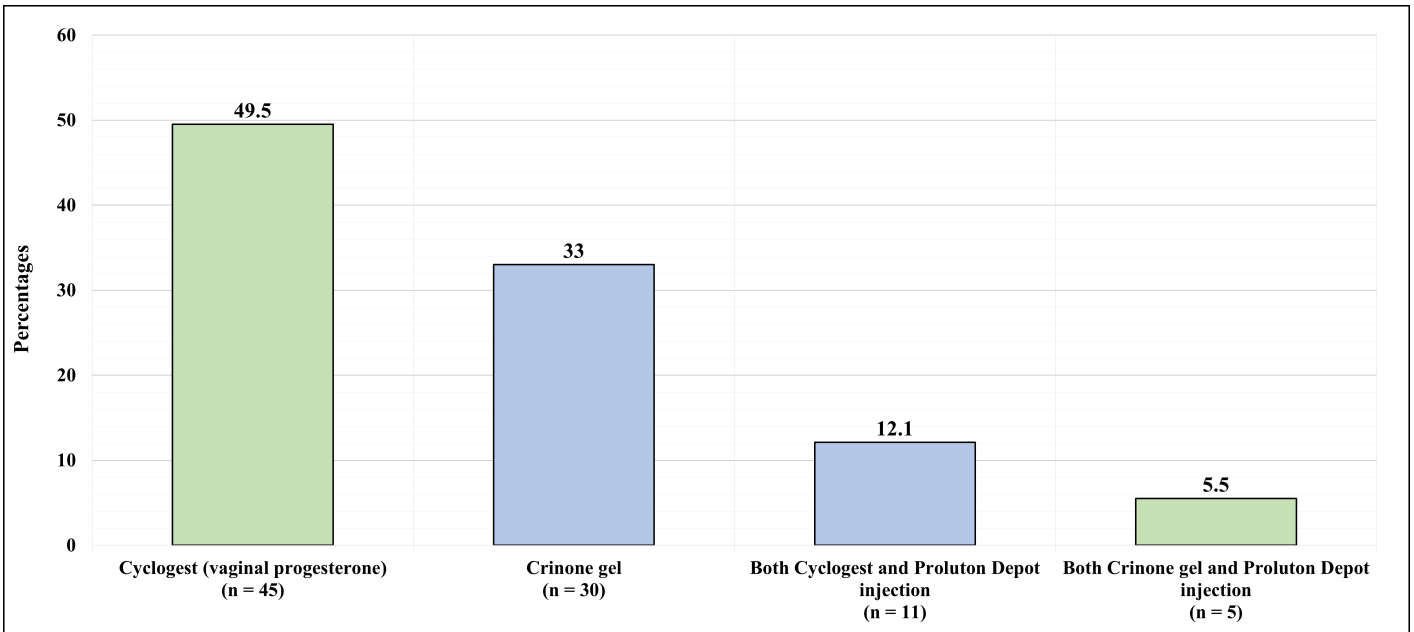

Figure 1, Type of Progesterone Used for Luteal Support

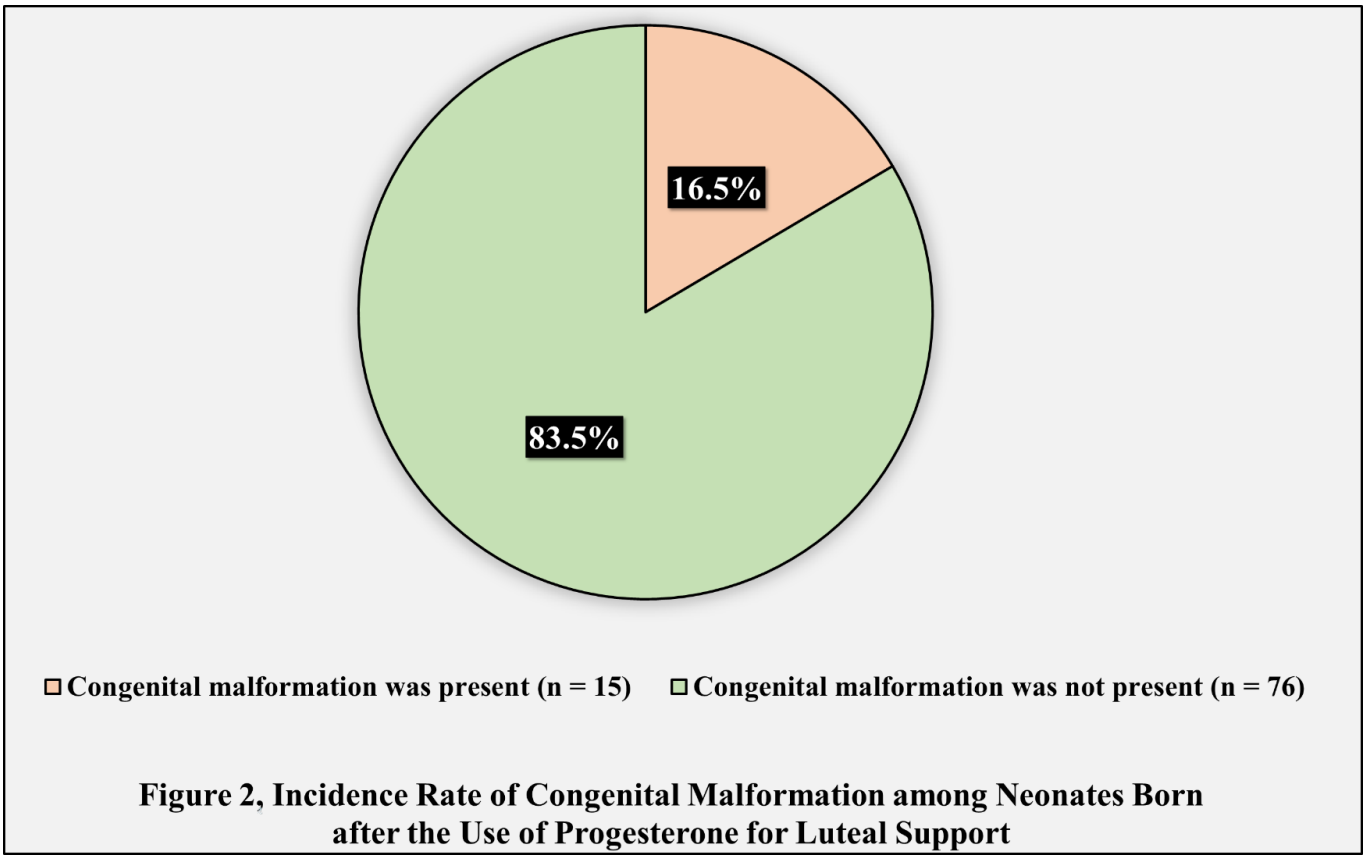

Figure 2, Incidence Rate of Congenital Malformation among Neonates Born after the Use of Progesterone for Luteal Support

Table 1. Congenital Malformation Present in Neonates.

Malformation	n	%
Patent ductus arteriosus	5	5.49
Delayed speech	2	2.20
Brachydactyly	1	1.10
VACTERL	1	1.10
Down syndrome	1	1.10
Alopecia	1	1.10
Epilepsy	1	1.10
Limping	1	1.10
Autism spectrum disorder	1	1.10
Myasthenia gravis	1	1.10
Polycystic kidney disease	1	1.10
Ambiguous genitalia	1	1.10
Oesophageal relaxation	1	1.10
Hydronephrosis	1	1.10
Undescended left testis	1	1.10
Right hydrocele	1	1.10
Cortication of the aorta	1	1.10
Hypospadias	1	1.10
Hearing loss	1	1.10

Table 2. Comparison of Congenital Malformation Incidence Across the Types of Progesterone given for Luteal Support.

Type of Progesterone	Incidence of Congenital Malformation		P-Value	Pearson Chi-Square Value	DOF
	Present	Not present			
Cyclogest	10 (22.2%)	35 (77.8%)	0.121	5.82	3
Crinone gel	1 (3.3%)	29 (96.7%)			
Both Cyclogest and Proluton Depot injection	3 (27.3%)	8 (72.7%)			
Both Crinone gel and Proluton Depot injection	1 (20%)	4 (80%)			

V. Limitations

This study has some limitations. The response rate was low, and data were retrieved from the patients themselves, making them subject to recall bias. Confounders should not be disregarded. Furthermore, this study was retrospective, so there were limitations to certain information. Recommendations for future studies would be to employ a better method to obtain data so as to avoid recall bias.

VI. Conclusion

No significant association was found between the incidence of congenital malformation and age or BMI. The most commonly noted congenital malformation was patent ductus arteriosus, followed by delayed speech. Brachydactyly, Down syndrome, autism spectrum disorder, and a number of other conditions were observed. Finally, based on our review, the number of congenital anomalies was similar between the groups (p=0.121).

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