Case Report

TNF-α Inhibitors Rescue APS-Induced Dangerous Pregnancies by Reducing the Risk of Miscarriage: A Report of 7 Cases

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TNF-α Inhibitors Rescue APS-Induced Dangerous Pregnancies by Reducing the Risk of Miscarriage: A Report of 7 Cases

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Abstract: Antiphospholipid syndrome (APS) is a group of autoimmune diseases caused by antiphospholipid antibodies (aPLs) characterized by arteriovenous thrombosis and a morbid pregnancy. We deliberated a case report of seven cases to investigate whether inhibitors of tissue necrosis factor-α could reduce pregnancy dangers caused by APS. The seven patients are with increased tumor necrosis factor, poor improvement after receiving traditional inhibitory drugs. To address these situations, the tumor necrosis factor inhibitors were prescribed after getting the patient's informed consent, and the state of illness was carefully watched for. After treatment, symptoms of contractions and abdominal pain disappeared and the B ultrasound examination showed embryo survived with good obstetric outcomes. Subsequently, maternal and neonatal health is compromised. An intervention by the administration of TNF-α inhibitors was posited to be an effective way of reducing dangerous pregnancies like preterm pregnancies, premature deliveries, abortions and miscarriages. We reviewed outcomes from seven cases in an attempt to establish how TNF- α Inhibitors could save pregnancies. We focused on key pregnancy outcomes like birth weight, gestational weeks and preterm miscarriage to tell the outcomes of TNF- α Inhibitors in pregnancy. After careful evaluation of the results surrounding these aspects, we found that TNF- α Inhibitors could prolong gestational period. Other positive outcomes include the attainment of birth weights approach the threshold, zero incidence of preterm miscarriage.

Keywords: antiphospholipid syndrome; TNF-α inhibitors; dangerous pregnancy; gestational weeks

Introduction

APS refers to an autoimmune condition known to cause pregnancy complications to line autoimmune thrombocytopenia, thrombosis, pre-eclampsia, fetal loss, or fetal growth restriction [1]. Obstetric complications caused by APS include oligohydramnios, recurrent miscarriage, premature and early delivery, fetal distress, neonatal or fetal thrombosis, intrauterine growth restriction, eclampsia, pre-eclampsia, HELLP syndrome, placental insufficiency, and venous or arterial thrombosis are the severe outcomes of APS in pregnancy [2]. The occurrence of these complications threatens both maternal and fetal health. The severity of these complications calls for an effective intervention to save pregnancies: the life of pregnant women and their infants.

Despite a lack of strong evidence on the treatment of APS in pregnancy, TNF-α inhibitors have been reported as possible and potent interventions [3,4]. Different TNF-α inhibitors have been reported to be well-tolerated. Notably, neither malformations in newborns nor implantation failures or miscarriages in the first trimester have been reported [3]. TNF-α inhibitors have been associated with few adverse effects among treated pregnant women, like miscarriage, which poses a significant

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health concern among women [5]. Miscarriage, alongside other pregnancy complications, has prompted the formulation of multiple interventions to save the lives of pregnant women and neonates.

There is an increase in the number of childbearing females treated with TNF-α inhibitors. In many patients, TNF-α inhibitors have been reported to be fast-acting, well-tolerated, and highly active. After decades of safety concerns issues, the Food and Drug Administration carried out a study and classified TNF-α inhibitors "Category B" in pregnancy. This classification suggested that animal studies in whom the studies had been performed reported no adverse effects or safety concerns [6]. In corroboration with FDA's declaration and reports from other studies, some investigations support the potency of TNF-α inhibitors and provide a rationale for their indication. An investigation by Clowse et al. reported TNF-α inhibitors neither caused teratogenicity effects nor increased fetal death, in contrast with the general population [7], as they have been linked with decreased miscarriages.

According to the revised Sapporo criteria for classification of the antiphospholipid syndrome, the disease is characterized by thrombosis, pregnancy complications, or both in patients with persistent antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, or anti-β2GPI antibodies[8]. The persistence of Antiphospholipid antibodies is known to cause venous and arterial thrombosis and loss of pregnancy. Anticardiolipin antibodies IgG or IgM (ELISA), anti-β-2glycoprotein-I antibodies IgG or IgM (ELISA), and lupus anticoagulants (functional essays) are the main Antiphospholipid antibodies [9–12]. The presence of lupus anticoagulants is the strongest risk factor for both arterial and venous thrombosis in APS. In several studies, it has been demonstrated that the risk of arterial and venous thrombosis increases with the number of positive tests for aPL, with the highest risks in patients with both LAC, aCL and anti-β2GPI antibodies, so-called 'triple positive patients' . In this case serious, we analyze and report the effects of TNF-α inhibitors in pregnancy. We will focus on TNF-α inhibitors' potency in saving pregnancy complications caused by APS. We will focus on TNF-α inhibitors' ability to relieve contractions. Hence, reducing miscarriages. The scope of the present study is investigating general outcomes of TNF-α inhibitors in the dangers of pregnancy caused by APS.

Case Descriptions

The basic features of the study participants in the present investigation include age, diagnostic time, height, weight, Body Mass Index (BMI), pre-treatment assessment outcomes, diagnosis, and the respective overall BMI status. First, the study participants were examined in different health facilities and at different times. We evaluated 7 cases and reported their features as age, year of diagnosis, weight, height and the BM (**Table 1**). The average age and BMI were 32 years and 26.72 kg/m^2. The reference point of BMI was 18.5 kg/m2 to 23.9kg/cm2（Chinese Population Obesity Criteria）. 7 women in two institutions were treated with TNF-α inhibitors.

Table 1. Basic features of the study specimen.

Case number	Year of diagnosis	age	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	2021	27	162	53	20.2 (normal)
2	2020	30	160	60	23.4 (normal)
3	2019	33	168	60	21.3 (normal)
4	2018, January	38	165	50	18.4 (mid thinness)
5	2018	34	153	80	34.2 (Obese class II)
6	2018, April	30	167	106	38.4 (Obese Class III)
7	2019	33	161	81	31.2 (Obese Class I)

Diagnostic Assessment

The diagnostic criteria for APS are based on the 2006 Sapporo International Classification Standard Sydney Revision. The diagnosis of APS has to meet at least 1 clinical criterion and at least 1

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laboratory criterion, besides, high antibody titer measurements must be carried out with an interval of at least 12 weeks. The clinical criteria include (1) vascular thrombosis: ≥1 arterial, venous or small vessel thrombosis of any tissue or organ (clearly found on imaging or histopathology), and there is no vasculitis in the vascular wall of the thrombus site; (2) Pathological pregnancy: ① ≥1 unexplained fetal arrest after 10 weeks of pregnancy (confirmed by ultrasound or direct examination). (2) ≥1 preterm birth caused by eclampsia, severe preeclampsia or severe placental dysfunction before 34 weeks of pregnancy. (3) ≥3 consecutive abortions of unknown cause within 10 weeks of pregnancy (excluding women's hormone levels, anatomical abnormalities and chromosomal abnormalities in both men and women).Laboratory criteria include (1) ≥2 positive lupus anticoagulant; (2) ≥2 medium/high titer IgG and/or IgM type aCL in serum or plasma (value> 40GPL/MPL or titer >99th percentile of the general population); (3) ≥2 times of medium/high titer IgG and/or IgM β2GPI antibody in serum or plasma (titer>99th percentile of the general population). Pathological pregnancies such as recurrent miscarriage, eclampsia, and placental insufficiency are called obstetric APS (OAPS). Some OAPS patients only meet typical clinical criteria, atypical laboratory criteria or typical laboratory criteria, atypical clinical criteria, which is called atypical OAPS (non-criteria OAPS, NC-OAPS). Patients in this research are classified according to OAPS, NC-OAPS and SN-APS.

Case Reports

Before the administration of TNF-α inhibitors, we examined seven women from two institutions: Hubei Provincial Hospital of Traditional Chinese Medicine Affiliated to Hubei University of Traditional Chinese Medicine, Cang zhou Hospital of Integrated TCM-WM Hebei. The other pre-treatment outcomes (Number of lost pregnancies and method of conception, etc) were compared with post-treatment observations.

Table 2 summarizes the clinical data of the examined women. The clinical data included the intervention during pregnancy, the TNFα inhibitors therapy, mode of delivery, TNF-α inhibitors usage in weeks and the gestational week, outcome measurements were taken and limited to the particular week indicated the in the table above. Inconsistent pregnancy outcomes could be attributed to the different treatment during pregnancy. Cases 1, 4, 6 and 7 were treated with LWMH, whereas cases2, 3 and 5 were treated with LWMH and aspirin (low-dose). Generally, the overall intervention in each case was unique since treatment, period of treatment and therapy varied across the board. We observed different fetal weight. In contrast to the normal fetal weight, the ideal point of reference of 2.5kgs to 4.0kgs. We did not observe fetal weight in case 6 and 7 as they were ongoing pregnancies. Nonetheless, case 1, 2, 4, and 5 reported fetal weight below the required threshold: 2.30kgs, 2.35kgs, 2.25/2.25kgs and 1.95kgs, respectively, case 3 reached the ideal threshold: 3.4kgs. Also, TNF-α inhibitor usage time (weeks) period varied in the seven cases. The least period of use of TNF-α inhibitor was 8+2, in case 1, and the highest were case 3 and 4, 27 and 26 weeks.

Table 2. Clinical data of the case reported analyzed in the present study.

Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Year of diagnosis	2021	2020	2019	2018	2018	2018	2019
Conception	NC	NC	NC	ART-FET	NC	NC	NC
TNF-α inhibitors therapy	Certolizumab pegol*1 dose	Certolizumab pegol*1 dose	Adalimumab *1 dose	Aspirin*2 dose	Adalimumab *1 dose	Certolizumab pegol*1 dose	Certolizumab pegol*1 dose

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Mode of delivery	Cesarean delivery	Cesarean delivery	Cesarean delivery	Cesarean delivery	Cesarean delivery	-	-
treatment during pregnancy	LWMH	LWMH and aspirin (low-dose)	LWMH and aspirin (low-dose)	LWMH	LWMH and aspirin (low-dose)	LWMH	LWMH
TNF-α inhibitor usage time (weeks)	8+2	17+2	27	26	16	13+2	15+3
Gestational age at birth(weeks)	33+1	38	37+1	37	32+5	24+1	16+4
Fetal weight (grams)	2300	2350	3400	2250/2250	1950	Ongoing pregnancy	Ongoing pregnancy
The fetus number	single birth	single birth	single birth	gameplay pregnancy	single birth	Monocyesis	Monocyesis
Previous obstetric history	MC*6	MC*5	MC*5	FL*3	FL*1	MC*4	FL*2

Note: FL, Fetal loss (> 10wks); MC, Miscarriage (<10wks): NC, Natural conception, ART: Artificial reproductive technology; FET, Frozen embryo transfer.

Outcomes of the case reports

These 7 cases focused the 4 study outcomes: term births, premature births, abortion, and extant children. We focused on preterm miscarriage. Participants in the two study centers reported successful sustained pregnancy after treatment. TNF-α inhibitors saved the pregnancies. The outcomes of these cases can be contrasted with post-treatment outcomes to establish the dangers averted by TNF-α inhibitors. Premature miscarriage are severe and unwanted incidences following and associated with pregnancy. Reduced premature pregnancies prolonged gestational weeks after treatment with TNF-α inhibitors. This was key to protecting maternal and neonatal health.

Table 3 reports detailed specimen data: age, pregnancy BMI, pre-existing diseases, endocrinology, Antiphospholipid syndrome, thrombophilia and other rheumatic diseases. These are key to determining maternal health status that inform whether pregnancy could be compromised or safety. Patient 1 was diagnosed with NC-OAPS, patient 5, 6, 7 were diagnosed with OAPS，and

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patient 2、3、4 were diagnosed with SN-APS (see Table 1). Cases 1 and 3 were diagnosed with Hashimoto and case 7 with PCOS.

Table 3. Detailed information of study specimen.

Patients	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Ages	27	30	33	38	34	30	33
Pre-pregnancy BMI	19.5	22.4	20.8	18.1	33.0	38.4	31.2
Preexisting disease	None	None	None	None	None	None	None
Endocrinology	Hashimoto	-	Hashimoto	-	-	-	PCOS
Antiphospholipid syndrome	NC-OAPS	SN-APS	SN-APS	SN-APS	OAPS	OAPS	OAPS
Other rheumatic diseases	no	no	no	no	no	no	no
Thrombophilia	no	no	no	no	no	no	no

Table 4 summarizes the differences between pre-and post-treatment TNF-α's levels in the blood (The measurable level was <8.1), timing of TNF-α inhibitors intervention and the results. Patient 4 took the longest period, 7 days, to report the disappearance of symptoms, followed by patients 1 and 5, and lastly, 2, 3, 6 and 7. The disappearance of symptoms of a risk pregnancy shows the effectiveness of the interventions. A decision can be made from these observations on the rationale of administering TNF-α inhibitors. After treatment, TNF-α decreased to varying degrees in all 7 patients, among which cases 1, 3, 6, 7 reached the ideal level (< 8.1) and case 5 reached the highest level (123.04). The gestational age at birth was reported, cases 6 and 7 were ongoing pregnancies, case 1 did not reach the ideal gestational age (37-42 weeks), and the rest of the fetuses were born to the desired gestational age.

Table 4. TNF-α's levels in the blood, timing of TNF-α inhibitors intervention and the results.

Patients	TNF-α inhibitors usage time (weeks)	TNF-α (< 8.1)		Time of symptom disappearance(day)	Gestational age at birth(weeks)
		Pre-treatment	Post-treatment		
1	8+2	42.2	7.81	2	33^{+1}
2	17+2	97.5	13.6	1	38
3	27	230	6.2	1	37^{+3}
4	26+5	183.46	35.39	7	37

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5	16	271.86	123.04	2	32^{+5}
6	13+2	＜2	＜2	1	24+1 Ongoing pregnancy
7	15+3	13.34	4.6	2	16+4 Ongoing pregnancy

Table 5 summarizes post-treatment outcomes in the seven cases, where the effect of TNF-α inhibitors were measures after delivery. Five out of the seven cases underwent caesarian delivery. The average height of the newborns was 48.20 centimeters, whereas the average weight was 2.50 kilograms. The biggest takeaway from this experiment regards the difference in the gestational period within which the newborns were delivered. The seven cases reported different gestational weeks, which had different additional days. Unfortunately, only 2 cases (all of them are ongoing pregnancy) of the 7 cases was not associated with caesarian delivery. The Apgar scores ranged between 8 to 10, whereas the height and the weights of the delivered children varied across the cases.

Table 5. A summary of the post-treatment pregnancy outcomes in the seven cases.

Patient	Gestational week	male	Female	Caesarian delivery	Height (cm)	Body weight(kg)	Apgar score
1	33+1	-	1	1	50	2.30	8
2	38	1		1	45	2.35	9
3	37+3	-	1	1	51	3.40	10
4	37	-	2	1	48	2.25/2.25	10
5	32+5	1		1	47	1.95	10
6	24+1, Ongoing pregnancy	-	-	-	NA	NA	NA
7	16+4, Ongoing pregnancy	-	-	-	NA	NA	NA

Discussion

As a multifactorial syndrome, abortion has complex etiology, and the causative factors include genetic inheritance, anatomical abnormalities, endocrine disorders, prethrombotic state, microorganisms, infections, mental psychology, environment, pathological expansion of the uterus, et cetera. Additionally, immune function abnormalities, immune inflammation, immune system activation or dysfunction occupy an important position in the occurrence of abortion and premature birth. Shortened pregnancy and the loss the pregnancy through resulting preterm miscarriage is a significant health concern. Progestogens such as oral dydrogesterone, intramuscular progesterone, or vaginal progesterone are often used; oxytocin receptor antagonists, such as atosiban; β - receptor agonists, such as ritodrine; inhibitors of prostaglandin synthesis such as indomethacin; and calcium channel blockers such as magnesium sulfate (MS), nifedipine. Resorcinol (not included in guidelines), a non-atropine, non-papaverine inophilic smooth muscle antispasmodic drug, is also currently used. Failure to respond to conventional treatment results in miscarriage. TNF-α inhibitors have been floated as potential interventions against early contractions that lead to premature miscarriage.

Tumor necros factor-alpha (TNF-α) is an inflammatory cytokine belonging to Th1 lymphocytes, which regulates the secretion of prostaglandin E2, human chorionic gonadotropin, serum human

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placental prolactin, progesterone and renin in the placenta, affects placental formation and embryonic development, and is a cytokine with pro-inflammatory and prothrombotic effects.

Table 1. summarizes the basic features of the study participants involved in the investigation. The basic features of the included participants included age, weight, BMI, height, health status before treatment with TNF-α inhibitors, the diagnosis, and overweight status. The average age of the pregnant women studied was 32 years, whereas their average BMI was 26.72 kg/m2. Participant features amounted to the varying outcomes, especially BMI. Nonetheless, Antiphospholipid syndrome was a common diagnosis among the studied participants. Further, table 4 provides detailed maternal data that affects pregnancy safety. We calculated the BMI in each case and found cases 1, 2, and 3 with normal BMI: 20.2 kg/m^2, 23.4 kg/m^2 and 21.3 kg/m^2, respectively. We observed one case of mid thinness, case 4, with a BMI of 18.4 kg/m^2, whereas the remaining three cases reported different classes of obesity. We found case 5 with Obese Class II: 34.2kg/m^2, case 6 with Obese Class III, with a BMI of 38.4 kg/m^2 and case 7 with Obese Class I, with a BMI of 31.2. In contrast to CDC's reference point of BMI, 18.5 kg/m2 to 23.9 kg/cm2, we could conclude that case 5, 6 and 7 were obese (**table 1**). From this analysis, the BMI of the participants involved in the present study did not affect the outcomes significantly.

The differences in gestational weeks was a fundamental observation. The seven cases reported different gestational weeks. **Table 5** summarized the gestational weeks and the birth weights of the newborns in each case. Different TNF-α inhibitor therapy were administered for different weeks within the gestation period. This could account for much of the differences in the observations. Nonetheless, the major outcome regards successful gestation since we did not observe preterm miscarriage. With reference to case 2 and 4, we established that gestational weeks was dependent on the length of use of TNF-α inhibitors: gestational weeks increased according to the period of use of the TNF-α inhibitors. The intervention was found to prolong gestation that would end in normal delivery, safely. **Table 4** summarizes the effect of TNF-α on the blood levels of the patients, we found that the levels of TNF-α were reduced to varying degrees in all patients, which can also be considered as a positive effect of the intervention. One study was carried out to establish TNF-α inhibitors' effectiveness against APS for pregnancy-related complications, the study reported that the outcomes had been enforced by many laboratories and medical institutions where women are diagnosed with such complications. Positive maternal and neonatal outcomes were found among women who received TNF-α inhibitors treatment [13]. We focused on gestational weeks, founded that TNF-α inhibitors have a positive effect on prolonging gestational weeks.

The emphasis put on the different gestational weeks and additional days does not imply that they should or ought to be similar. However, they ought to have been relative to each other. Individual differences and characteristics can be put across to cancel out the difference in gestational week's factor. Despite the major differences in gestational weeks, we found that existing literature contest that TNF-α inhibitor treatment contributes to the attainment of an average birth weight of approximately 2.5~4.0kg [14,15]. We found that all newborns approach the fetal birth weight, 2.5 to 4.0 kg. We did not measure the brith weight in case 6 and 7 as it was ongoing pregnancy. Case 1, 2, 3, 4, 5 were found with a birth weight (**Table 5**). These observations support the argument that TNF-α inhibitors could save pregnancy dangers by increase gestational weeks.

We found positive outcomes of TNF-α inhibitors intervention during pregnancy. Of great significance was the increased birth weight, increase gestational weeks, and successful pregnancy. Except case 6, 7 (ongoing pregnancy), none of the 5 cases reported preterm miscarriage, case 6 and 7 are ongoing-pregnancy, However, the decrease in TNF-α indicates the effectiveness of TNF-α inhibitors, and, there were no dangerous pregnancy manifestations as of the time of reportin.; therefore, we can assume that TNF-α inhibitors prolong the gestational week by decreasing the level of TNF-α. Arguably, this is a fundamental outcome of the intervention since maternal and neonatal life was protected. Often, preterm miscarriages lead to the loss of neonatal life or can require a caesarian section to save maternal or neonatal life [16,17]. In our analysis, we did not observe a case where a cesarean procedure was required to save neonatal or maternal life. Instead, this is all due to maternal subjective factors (e.g., pain, fear), so we can categorize this outcome as a specific factor.

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Conclusion

We studied the outcomes of TNF-α inhibitors in efforts to save pregnancy dangers associated with APS and found compelling outcomes. The outstanding observation concerns the dynamic nature of the outcomes from the seven cases. We focused on pre-gestational and gestational BMI, birth weights and the overall gestational weeks. We observed dynamics and different outcomes in the seven cases. Importantly, the therapy period, the treatment and the TNF-α inhibitors usage time (weeks) varied. **Table 2** shows the different TNF-α inhibitor used in each case, whereas **table 2** and **4** shows the different period of use. We could attribute the inconsistent treatment options and periods to the differences in the outcomes and the resulting gestational weeks. The argument floated, based on these observations, is the varied use of TNF-α inhibitors, in terms of particular drug used in therapy, patient features and the different gestational weeks within which the drugs was administered, accounted for the different outcomes.

Even though the general outcome of TNF-α inhibitors intervention against pregnancy dangers stands out, caution must be taken when interpreting the outcomes of this case report. The differences in the effects are consistent across the 7 cases. This includes the gestational weeks within which the deliveries were achieved, the percentages by which the major pregnancy dangers were decreased, and the degree by which Antiphospholipid antibodies were decreased. Of course, a scientific study could attribute these factors to particular causes. Individuality and patient characteristics could be a potential reason for this phenomenon in the present study.

We concluded that the present study reported compelling evidence pointing at TNF-α inhibitors' effectiveness in reducing pregnancy dangers caused by APS based on key pregnancy outcomes. The average birth weight was achieved among infants born after the intervention. From this outcome, we concluded that TNF-α inhibitors could save neonatal and maternal health.

Despite focusing on the outcomes obtained from the intervention by different medications in the TNF-α inhibitors class, we found strong evidence addressing the primary objective of the present study. This case report demonstrates the outcomes of TNF-α inhibitors in saving dangerous pregnancies associated with APS.

Patient Perspective

Study participants agreed to take part in the present study, having acknowledged the clinical outcomes and significance of the intervention. And agreed to disclose the results of this study without disclosing the patients' personally identifiable information. Informed consent for publication will be provided to patients upon request.

Ethical Considerations

Ethical principles steered our investigation. All seven participants appended their signatures that they willingly participated in the present study. The participants' identities will be concealed and kept confidential. The respective Ethical committees of the institutions where the studies were carried out were involved to ensure the enforcement of other ethical principles protecting the participants.

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