**Heparin Treatment for Pregnant Women with Protein S Deficiency: A Systematic Review**

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Funding: None

Conflict of Interest: None

Word Count – Abstract: 111

Word Count – Main Text: 997

References: 15

**Abstract**

**Objective:** To evaluate the effectiveness of heparin for decreasing adverse pregnancy outcomes in women diagnosed with thrombophilia disorders, with an emphasis on protein S deficiency.

**Methods:** Literature was gathered using PubMed and CINAHL databases on the effectiveness of heparin on protein S deficiency during pregnancy.

**Results:** Most studies supported heparin as an effective intervention for preventing adverse pregnancy outcomes. One study showed no significant difference when heparin was compared to aspirin as an intervention.

**Conclusion:** Heparin is promising as an intervention for PS deficiency and other thrombophilia in pregnant women. Heparin and other interventions should be researched further as treatment options to protect the mother and fetus in a hypercoagulable state.

**Introduction**

Protein S deficiency is a blood clotting disorder with mild deficiencies affecting approximately 1 in 500 individuals and the prevalence of severe deficiencies unknown due to no diagnosis or misdiagnosis.1,2 The deficiency of protein S (PS), a clotting factor that regulates blood coagulation, causes an increased risk of blood clotting and is primarily congenital in an autosomal dominant manner.3 PS deficiency is one of many inherited hypercoagulable conditions with life threatening risks from developing blood clots including pulmonary embolisms and deep vein thromboses.4 The significant reduction in protein S levels during normal pregnancy make it both difficult to diagnose PS deficiency during pregnancy and put mothers with a deficiency at higher risk of complications.5 These complications include a variety of adverse outcomes, primarily a significant association between protein S deficiency and non-recurrent fetal loss after 22 weeks.6

Currently, there is little research geared towards inherited thrombophilia, specifically protein S deficiency, during pregnancy and treatments aimed at reducing complications, including fetal loss, blood clots, strokes, and death. Warfarin is an anticoagulating drug that has been used in clinical settings for over 50 years to reduce blood clots, but its use during pregnancy is strongly linked to stillbirth, spontaneous abortion, neonatal death, premature delivery and a variety of congenital anomalies known as fetal warfarin syndrome (FWS).7,2 A further study suggests that pregnant women who receive a form of the anticoagulant heparin, an alternative to warfarin, experience less adverse pregnancy outcomes than those patients who forgo heparin treatments, making it an important preventative drug for the safety of pregnant women with thrombophilia disorders.2

The objective of this systematic review is to evaluate the effectiveness of heparin for decreasing adverse pregnancy outcomes in women diagnosed with thrombophilia disorders, with a greater emphasis on protein S deficiency. An understanding of PS deficiency in pregnant women and the effects of heparin drugs on thrombosis outcomes will allow care providers to better understand effective responses and treatments for these patients.

**Methods**

***Search Strategies.*** Primary research was completed in September and October of 2021 using PubMed and CINAHL databases. CINAHL did not yield any new sources in addition to PubMed and will not be included in Figure 1 below. Search terms used in the databases were:

Keywords: ((protein s deficiency[Title/Abstract]) AND (heparin[Title/Abstract] OR enoxaparin[Title/Abstract])) AND (pregnancy[Title/Abstract])

The search was limited to studies pertaining to pregnant women with PS deficiency who were treated with heparin.

***Definitions***. Heparin comes in a variety of forms. This study does not differentiate between enoxaparin, nadroparin, certoparin, and unfractionated heparin.

**Search Results**

PubMed database searches yielded 3 relevant studies in which results for protein S deficiency can be extracted from the data. An additional 4 studies included PS deficient individuals in their studies. Database searches resulted in a total of 7 relevant studies, shown in Figure 1.

Figure 1. Flowchart representing article selection process.

**Results**

The primary sources in this review include a prospective evaluation study,8 a historical control cohort study,9 and a prospective study.10 The additional four studies included a randomized control trial,11 a multicenter randomized control trial,12 a retrospective, observational trial,13 and a preliminary study.14 Within the three primary studies comparing LMWH to aspirin, there were inconsistent results. Two suggested a positive heparin influence on live birth weight8,9 and neonate weight,8 while the other showed no significant difference between heparin and aspirin.10 The other studies consistently suggested that heparin is effective in decreasing a variety of negative pregnancy outcomes in patients. The randomized control trial comparing effects of low dose aspirin to a combination of enoxaparin and aspirin did not show a significant difference in perinatal and prenatal outcomes, but the heparin intervention group did have a significantly lower uterine artery pulsatility index (PI) which is associated with decreased risk of preeclampsia.11 The multi-center randomized control trial showed that LMWH with aspirin was more successful than aspirin alone in decreasing recurrence of HD before 34 weeks.12 The observational trial determined certoparin effective in preventing thromboembolism and reducing spontaneous abortion rates.13 The preliminary study showed that birth weights for protein S deficient and protein C deficient patients were slightly higher when treated with heparin than aspirin.14

**Discussion**

The results of this systematic review advocate for the use of heparin during pregnancy for those with Protein S Deficiency and other thrombophilia. Of the three primary studies, two showed at least one positive outcome of heparin for those with PS Deficiency8­,9 and the other showed no significant difference.10 Of the studies reviewing heparin on all thrombophilia, heparin interventions resulted in at least one positive outcome for both mother and child, including uterine artery pulsatility index, recurrence of HD, live birth rate, neonate weight, and thromboembolism prevention.15,12,13,14

Heparin appears to be a promising alternative to warfarin and more effective than aspirin in preventing adverse pregnancy outcomes. Heparin interventions result in positive outcomes related to complications of PS Deficiency and other thrombophilia, while avoiding the damage that warfarin imposes on the fetus.7 The diversity in study population reflects effective outcomes of heparin across ethnic groups.

Of the PS deficient specific research, two trials were experimental8,10 while the third was observational.9 Of the four additional studies, the two strongest were randomized control trials.15,12 The third was an experimental study14 and the last was a observational trial.13 All studies lacked large sample sizes with 50 or fewer PS deficient patients. Future clinical trials should focus specifically on PS deficient patients, or isolate results from this population.

The findings of this systematic review should be disseminated to obstetricians and other members of delivery care teams to increase awareness of possible interventions during PS deficient pregnancies. Most studies suggest that medical practice should add heparin to intervention regimens of pregnancy in Protein S deficient women, but further studies need to be performed with larger study populations and directly assessing thrombosis outcomes for PS deficiency. Future research on the topic should address proper dosage, heparin as a singular intervention or mixed with additional drugs, and the proper gestational period to receive treatment. Ultimately, one dose of heparin daily during pregnancy is successful in lowering pregnancy complications associated with the hypercoagulable disorders.

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| **Table 1. Summary of Studies Reviewed** | | | | |
| **Source** | **Context** | **Design** | **Intervention** | **Results** |
| Bar et al. (2000)1 | Petah Tikvah, Israel  65 patients, 22 with Protein S Deficiency, 14-24 weeks gestation with 3 or more miscarriages, intrauterine growth restriction (IUGR), and preeclampsia between October 1996 and October 1998. | Randomized control trial testing effectiveness of low-dose aspirin plus low molecular weight heparin (LMWH) or low-dose aspirin on fetal and maternal Doppler flow parameters. | Those with a thrombophilia received 100mg/day of low-dose aspirin and 40mg/day of enoxaparin. The other patients received only low-dose aspirin. | The group receiving LMWH showed no significant decrease (P>0.5) in maternal and perinatal outcomes (preeclampsia, caesarean section, gestational week of delivery, birth weight, IUGR, neonatal hospitalization rate) however they did show a significant decrease (P=.006) in uterine artery pulsatility index (PI) while those given aspirin had nonsignificant changes. |
| De Vries et al. (2012)2 | The Netherlands, Australia, Sweden  128 subjects, 24 with Protein S Deficiency, a history of uteroplacental insufficiency, HD, and chronic hypertension between December 2000 and December 2009. | Multicenter randomized control trial to test whether adding LMWH to aspirin before 12 weeks into the pregnancy decreases the recurrence of hypertensive disorders (HD). | Subjects were randomized to receive either 5000IU of dalteparin with 80mg aspirin daily or just 80mg aspirin daily. dalteparin was adjusted based on weight. | LMWH with aspirin decreased recurrence of HD before 34 weeks’ gestation (P=0.012). There was no significant difference between the groups for secondary outcomes (gestational weight, abortion, pre-eclampsia, HELLP syndrome, and a variety of side effects). |
| **Gris et al. (2004)**3 | **Languedoc-Roussillon Region, France**  **160 patients with ≥ 1 pregnancy loss (PL), 28 with PS Deficiency.** | **Prospective evaluation study to compare aspirin with enoxaparin to improve live birth outcomes.** | **Patients were either given 100mg daily of low-dose aspirin or 40mg daily of enoxaparin.** | **Enoxaparin group had higher live birth rates than aspirin (P=0.0006) for PS Deficiency specifically. The population showed a higher neonate weight for those treated with enoxaparin than in the aspirin group (P=0.0005).** |
| Grünewald et al. (2021)4 | Heidenheim, Germany  74 pregnancies, 6 with PS Deficiency from 2009 to 2019. | Single center, retrospective, observational trial observing those receiving certoparin. | Study observed 74 pregnancies receiving a dose of 8,000 IU of certoparin daily. | Certoparin was determined effective in preventing thromboembolism and reducing spontaneous abortion rates.  No P-Values Available. |
| Riyazi et al. (1998)5  Preliminary study to De Vries et al. | Amsterdam, The Netherlands  26 patients (18 Protein S deficient) found with previous pregnancy, coagulation abnormalities, and preeclampsia or isolated fetal growth restriction were tested between January 1993 and January 1996. | Preliminary study to evaluate the effects of LMWH and aspirin on pregnancy outcome for women with homeostatic abnormalities. Those with abnormalities were compared to those without abnormalities but had similar pregnancy outcomes. Those without abnormalities received only aspirin. | 26 women were treated with heparin or aspirin. | 38% patients with abnormalities and 32% without abnormalities had preeclampsia. None had abruptio placenta. Birth weights for protein S deficient and protein C deficient patients were significantly higher than those who were treated with aspirin. (0.019). |
| **Shen et al. (2016)**6 | **Taiwan**  **50 women with PS deficiency and recurrent pregnancy loss (RPL) between 2011-2016.** | **Historical control cohort study to determine effect of LMWH on live birth rates.** | **Patients who lost a pregnancy while receiving low-dose aspirin then received 1mg/Kg or enoxaparin every 12 hours from beginning of enrollment to a few days before their next birth.** | **There were 47 successful livebirths. 12 had successful livebirths with aspirin, and with the following second pregnancies, only 3 resulted in abortion (due to aneuploidy pregnancy).**  **No P-Values Available.** |
| **Shinozaki et al. (2016)**7 | **Kobe, Japan**  **38 women with PS Deficiency and RPL between June 2009 and March 2014.** | **Prospective study to compare aspirin with unfractionated heparin to determine effect on birth week, birth weight, and pregnancy complications (fetal growth restriction, pregnancy induced hypertension, preterm delivery)** | **Patients either received 81mg of aspirin daily until 27 gestational weeks (GW) or 5,000-10,000 units of unfractionated heparin daily until 36 GW.** | **For those without a PL and only PS Deficiency, there was reportedly no significant difference (no p-value provided) between those who received aspirin and those receiving LMWH.** |