Thrombosis Research 170 (2018) 38–44

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Tinzaparin for the treatment of foetal growth retardation: An open-labelled randomized clinical trial☆

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ARTICLE INFO

Keywords:
Birth weight
Foetal growth retardation
Heparin, low molecular weight
Placenta, thrombosis
Randomized controlled trial

ABSTRACT

Objective: Foetal growth retardation (FGR) is a leading cause of perinatal death and long-term harms at survivors. Placental infarction plays a role in FGR, yet, no trials have evaluated whether low molecular weight heparins increase birth weight in ongoing FGR pregnancies.

Methods: An open-labelled randomized trial in Denmark during 2011–2016, including singleton pregnant women with FGR (estimated foetal weight < 2.3 percentile) diagnosed before gestational weeks 32. Participants were randomly assigned using sealed, blinded envelopes 1:1 to tinzaparin (4500 IU daily until 37 gestational weeks) or no tinzaparin. The primary outcomes were the observed birthweight relative to the expected for gestational age and gender, and foetal growth rates in the two trial groups evaluated by an *intention to treat* analysis.

Results: We enrolled 53 women. The mean gestational age was 261 days in the tinzaparin group and 246 days in the no treatment group. The mean birth weight was 2229 g in the tinzaparin group compared to 1968 g in the no treatment group. However, the birth weight relative to the expected from gestational age and gender was only 2.5 percentage points higher in the tinzaparin group [−5.1 to 10.0] ($p = 0.51$). The foetal growth rate during follow-up was 124 g/week in the tinzaparin group and 119 g/week in the no treatment group, a difference of 5 g/week [−19 to 29] ($p = 0.67$). Two perinatal deaths both occurred in the no treatment group.

Conclusion: We found no evidence of a tinzaparin effect on the foetal growth rate or the birth weight after adjustment for gestational age.

1. Introduction

Worldwide, foetal growth retardation (FGR) is a leading cause of perinatal death and long-term harms for the survivors [1,2]. Furthermore, also the consequences of prematurity challenge these new-borns, as premature delivery is yet the only treatment option. A cornerstone among the pathophysiologic pathways leading to FGR is placental vasculopathy with placental infarction and impaired blood flow in the utero-placental vessels [3,4]. Therefore, anticoagulant drugs may constitute a principle of treatment and among these, low molecular weight heparins are the drugs of choice during pregnancy because they do not cross the placenta, have a favourable safety profile for the mother, and a predictable anticoagulant effect [5,6,7]. When used as a prophylactic intervention in pregnant women with a prior FGR pregnancy, low molecular weight heparins seems to increase birth weight in subsequent pregnancies [8,9,10]. Furthermore, low molecular weight heparins decrease the uterine artery resistance in hypertensive pregnancies [5,7,12], a mechanism from which also FGR pregnancies may benefit [13,14,15]. However, identification of women at risk of developing FGR is difficult.

Yet, there is no evidence on the effect of low molecular weight heparin treatment for FGR diagnosed in ongoing pregnancies. To

☆ Trial registration. ClinicalTrials.gov (EudraCT no. 2011-000818-20).
Funding. The Danish Council for Independent Research (0602-02173B FSS) and Central Region of Denmark. Leo Pharma donated the trial drug.
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https://doi.org/10.1016/j.thromres.2018.08.006
Received 19 May 2018; Received in revised form 12 July 2018; Accepted 8 August 2018
Available online 10 August 2018
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address this gap in knowledge, we conducted a randomized trial testing if the low molecular weight heparin, tinzaparin, improves birth weight in ongoing pregnancies complicated by foetal growth retardation. We hypothesized that low molecular weight heparin increases foetal growth in ongoing pregnancies complicated by FGR.

2. Methods

2.1. Setting and study design

We conducted an open-labelled randomized controlled trial at three obstetric centres in Denmark (Aarhus University Hospital, Regional Hospital Randers, and Regional Hospital Herning). The trial was monitored by the Good Clinical Practice Unit at Aarhus University Hospital, Denmark according to "Guideline for good clinical practice for trials on pharmacological products", World Health Organization, WHO Technical Report Series no 850, 1995, annex 3. The trial was registered in ClinicalTrials.gov (EudraCT no. 2011-000818-20).

2.2. Participants

In the period from November 2011 to August 2016, we included singleton pregnancies diagnosed with FGR before 32 gestational weeks. FGR was defined as an estimated foetal weight below the 2.3 percentile (−2.0 standard deviations (SD); −22% of expected weight corrected for gestational age) with or without increased uterine artery resistance [16]. Increased uterine artery resistance was defined as a mean pulsatility index > 1.7 after gestational weeks 24 [14,15]. We made use of fixed prophylactic dosage of tinzaparin in women with a pre-pregnancy weight between 50 and 90 kg; 4500 international units tinzaparin daily [17]. Therefore, women with a pre-pregnancy weight above 90 kg were not eligible for the present trial [17]. All women attending the Danish antenatal care programme undergo a first trimester risk calculation including ultrasound scan and biochemical markers with predictive value for Down's syndrome. At this ultrasound scan, the crown-rump length is determined as well as a precise gestational age. All participants had this first trimester scan including crown rump length and nuchal translucency measurements as well as risk calculation according to Foetal Medicine Foundation standards, and estimated due date was in all cases calculated from the crown rump length measurement [18]. All study criteria for inclusion and exclusion of trial candidates are shown in Table 1.

Table 1
Inclusion and exclusion criteria for the trial.

Inclusion criteria
1: Singleton pregnant
2: Able to read and understand the written informed consent
3: Foetal growth retardation; estimated foetal weight at least ≤ −22% of expected weight according to gestational age (≈2.3 percentile)
with or without
Pathologically increased resistance in the uterine arteries; mean pulsatility index > 1.7 standard deviations after gestational weeks 24.
In the initial protocol (before trial conduct was commenced), pathologically increased resistance in the uterine arteries from gestational week 19–20 was a separate inclusion criteria.

Exclusion criteria
1: Age < 18 years
2: Pre-pregnancy maternal body weight > 90 kg
3: Unable to read and understand the written informed consent
4: Renal insufficiency (plasma creatinine > 150 μ/L)
5: Pre-existing hypertension (systolic/diastolic blood pressure > 140/90 mm Hg)
6: Diabetes type I and II
7: Active inflammatory bowel disease
8: Severe heart disease
9: Abuse of alcohol or any drugs
10: Known bleeding disorder (von Willebrand disease, thrombocytopenia, haemophilia)
11: Ongoing treatment with vitamin K antagonists
12: Known allergy to low-molecular weight heparins
13: Previous heparin induced thrombocytopenia (type II)
14: Serious bleeding within the last month
15: Pre-existing indication for anticoagulant prophylaxis with low-molecular weight heparin in current pregnancy
16: Foetal chromosome anomaly
17: Severe foetal malformations
18: Contraindication for tinzaparin
19: Gestational week > 32 weeks

Criteria for exclusion from the trial
1: Development of thrombocytopenia, platelet count < 80×10^9/L
2: Allergic reactions to tinzaparin
3: Bleeding requiring hospital admission
4: Non-adherence to study protocol or withdrawal of written informed consent
6: Indication for treatment with a low-molecular weight heparin in current pregnancy
7: Identification of foetal chromosome anomalies
8: Identification of severe congenital foetal heart disease

2.3. Primary outcome

The primary outcomes were the observed birthweight relative to the expected for gestational age and gender, and foetal growth rates in the two trial groups.

Secondary maternal and foetal outcomes are presented in Table 3.

2.4. Trial drug and randomization procedure

Upon inclusion, we randomized participants in a 1:1 ratio to either tinzaparin (Innohep®, Leo Pharma, subcutaneous self-injection of 4500 international units daily until completed 37 weeks of gestation) or no tinzaparin (standard procedure), using sealed and blinded randomization envelopes generated from Aarhus University Hospital Pharmacy, Denmark. The randomization numbers were ordered in blocks of 10 (five numbers assigned to tinzaparin treatment, five numbers assigned to no treatment). Participants assigned to tinzaparin treatment self-injected the trial drug subcutaneously in the periumbilical area. We blinded the outcome adjudicators to the allocation but not the participants and the treating doctors. For safety reasons, we measured plasma creatinine and platelet count at inclusion and we observed the participants for potential allergic reactions the first 30 min after the first drug injection. We repeated the platelet count after 1–2 weeks to ensure identification of heparin-induced thrombocytopenia. Furthermore, we advised the obstetricians to wait at least 12 h from the last tinzaparin injection to performing a caesarean section or spinal or epidural analgesic procedures.

The participants attended follow-up visits every second week, where an obstetrician specialized in foetal medicine [18] conducted a transabdominal scan. This scan included an estimate of the foetal weight and consecutive Doppler assessments of the utero-placental flow if considered necessary by the obstetrician according to local foetal-medicine guidelines. The Doppler assessment was evaluated by pulsatility indices for the umbilical, uterine, and cerebral arteries [15,19]. Furthermore, a research technician drew a blood sample and obtained an interview according to a systematic case report form; evaluation of adherence to the trial drug, possible side effects, and exclusion criteria. In Denmark, the ultrasound-based monitoring of foetal weights is performed using Marsal's growth charts expressed as percentage deviations in estimated foetal weights according to a gender-specific and gestational age-specific reference curve [16,20]. Data from all scans were stored at the Danish Foetal Medicine Database from which we obtained the estimated foetal weight deviation according to gestational age, expressed as percentage deviation from expected for gestational age [16,22]. All scans were conducted using GE Voluson E8 or E10 ultrasound scanners using curve-linear abdominal probes (GE, Milwaukee, USA).

After delivery, placental pathology examination was performed following standard procedures [23]. The pathologist was blinded to

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