

Evaluation the Efficacy of Aspirin and Low Molecular Weight Heparin in Patients with Unexplained Intrauterine Growth Restriction accompanied by Early Onset Oligohydramnios

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Abstract:

The roles of inflammatory cytokines and local placental thrombosis in patient with unexplained intrauterine growth restriction (IUGR) accompanied by early onset oligohydramnios have been shown. Since low molecular weight heparin (LMWH) and aspirin have both anti-inflammatory and anti-coagulant effect, we evaluated their efficacy in patient with unexplained IUGR accompanied by early onset oligohydramnios.

Methods: A prospective comparative study that conduct at the department of obstetrics and gynecology at bint AL huda teaching hospital in Thiqr city between the 1st of march 2012 to the 1st of march 2013 in which (80) patients aged between (20 – 37) years old with unexplained IUGR and oligohydramnios referring to participated in our study, patients were divided into two groups, the thromboprophylaxis group (n=40) who received aspirin (80 mg PO daily) and LMWH enoxaparin (40 mg SQ once daily), the other group (n=40) was the control group who received no treatment apart from the usual protocol that are used for management of IUGR and oligohydramnios which involve frequent follow up. Live birth rate, obstetrical complications, prenatal complications and hemorrhagic side effect were recorded.

Result: There was no significance difference regarding the age, parity, BMI, gestational age at time of involvement in both groups. The rate of successful pregnancy was (75%) and (37.5%) in the treatment and control group respectively. So the thromboprophylaxis group had a higher rate of live birth than control group ($P < 0.05$). In thromboprophylaxis group (12.5%) patients and in the control group (37.5%) patients had intrauterine fetal death during the period of follow up. There were no significant difference in the number of preterm deliveries between the two groups, no maternal or fetal side effect was seen.

Conclusion: Aspirin and LMWH are successful in treatment of IUGR accompanied by early onset oligohydramnios by increasing the rate of live birth with few side effects for both the mother and fetus.

Introduction:

Early onset fetal growth restriction accompanied by severe oligohydramnios is an ominous pregnant complications with high perinatal morbidity and mortality of (80%-90%) if observed in the second trimester ⁽¹⁾. However, there is no promising modality to cure severe oligohydramnios during this period.

An important consideration is to ensure that reasonable efforts are made to identify and manage pregnancies affected by IUGR. While most IUGR discovered during the third trimester is due to a degree of placental insufficiency, therefore they has a good prognosis, care must be taken to consider the maternal, fetal and placental factors determining the likely etiology of IUGR during the antepartum period is important to reduce the rate of preventable death especially stillbirth of normally formed fetuses ⁽²⁾.

The fetal weight is determined by the genetic growth potential, the health of the fetus, the capacity of the mother to supply adequate substrates required for growth and ability of the placenta to transport these nutrients to the fetus. The majority of conditions affecting fetal growth are placental or fetal in origin. The most common placental conditions are alterations in the utero-placental and fetal-placental circulations. In majority of these cases, there is diminished maternal utero-placental blood flow,

caused by insufficient or incomplete trophoblastic invasion of the spiral arteries in the placental bed ⁽³⁾.

In order to diagnose IUGR it is essential to estimate gestational age, usually is calculated from last menstrual period, although it is unreliable because ovulation time is variable and we depend on first trimester ultrasound to date the pregnancy more accurately. Serial fundal height is essential in diagnosis together with ultrasound biometry including biparietal diameter, head circumference, abdominal circumference and femur length are recorded.

Amniotic fluid derived from fetal urine and from respiratory tract. In IUGR, shunting of blood from the splanchnic circulation results in reduced renal blood flow and hence less liquor. The amniotic fluid index is measured by adding the vertical depth of cord free amniotic fluid pools in each four uterine quadrants. A combined depth of 5 cm or more is normal. Also a single vertical pocket of amniotic fluid more than 2 cm is considered as normal. Another clue to the presence of IUGR is the presence of placental calcium deposits, finding of grade 3 placenta before 36 weeks is an evidence of IUGR ⁽⁴⁾.

A prospective trial by Zimmernann et al ⁽⁵⁾ evaluated the value of uterine artery Doppler performed between 21 weeks to 24 weeks in prediction subsequent development of IUGR,

persistent notching or elevated RI in the uterine arteries were define as pathological Doppler signs. Based on currently available data, there is insufficient evidence to recommended uterine artery Doppler as screening for all pregnancies but it can performed in high risk pregnancy.

Oligohydramnios is define as too little amniotic fluid. Normal amniotic fluid volume changes with gestational age and ways of accurately estimating it have changed over the years ⁽⁶⁾. It has been described as : amniotic fluid volume of less than 500 ml at 32-36 weeks of gestation, maximum vertical pocket (MVP) of less than 2 cm, amniotic fluid index (AFI) of less than 5 cm, or less than the 5th percentile.

Measurement of amniotic fluid volume by ultrasound include measurement of maximum vertical pocket depth and the summation of the depth of largest vertical pocket in each quadrant which called Amniotic Fluid Index (AFI), the four measurement are summed to obtain the AFI. A meta-analysis of randomized controlled studies has conclude that maximum vertical pocket (MVP) measurement during fetal surveillance seems better choice ⁽⁷⁾. The use of amniotic fluid index increases the rate of diagnosis of oligohydramnios and the rate of induction of labor without improvement in peripartum outcomes ⁽⁸⁾. The assessment of amniotic fluid volume (AFV) is important in pregnancies complicated by abnormal

fetal growth or IUGR. Oligohydramnios is a frequent finding in pregnancies involving IUGR and is more likely due to decrease fetal blood volume, renal blood flow and fetal urine output. Pregnancies complicated by severe oligohydramnios have been shown at increased risk of fetal morbidity.

Use of low dose of aspirin and low molecular weight heparin (LMWH), Enoxaprin is safe in pregnancy and it improved fetal outcome ⁽⁹⁾. Bleeding is a potential complication of anti-coagulant therapy and heparin induce thrombocytopenia has been observed less commonly in patients treated with LMWH. LMWH do not cross placenta and therefore are not associated with bleeding in fetuses and have no teratogenic effects ⁽¹⁰⁾. LMWH have higher specificity for Xa and have fewer effects on platelet activity. As a result LMWH may cause bleeding less often, while still having anti-coagulant effects. LMWH are associated with less risk of heparin induced osteoporosis.

The use of low dose aspirin for the prevention and treatment of pre-eclampsia and IUGR has been evaluated extensively. Leitch et al ⁽¹¹⁾ performed a meta-analysis of low dose aspirin for the prevention of IUGR. The use of aspirin showed a significant reduction in IUGR and non-significant reduction in perinatal mortality. Subgroup analysis revealed that aspirin was effective at low dose between 50 mg_80 mg per a day, but

the prevention effect at higher doses between 100 mg_150 mg per a day.

The authors conclude that low dose aspirin should not be used routinely in pregnant women. The indications for the use of low dose aspirin include preexisting chronic hypertension, recurrent pre-eclampsia and hypertension prior to 20 weeks and associated autoimmune disorder such as SLE and ant-phospholipid syndrome.

A multi-centric study FLASP (FOGSI Low Dose Aspirin Study) was carried out by FOGSI to assess the efficacy of low dose aspirin for prevention and treatment of pre-eclampsia and IUGR. The incidence of IUGR and pre-eclampsia were significantly decreased in patients who received prophylactic low dose aspirin prior to 16 weeks gestation. One of the largest collaborative studies was CLASP- Collaborative Low Dose Aspirin Studies in pregnancy. This study recommended the use of low dose aspirin in women liable to early onset pre-eclampsia severe enough to need preterm delivery.

Method:

A prospective comparative study that conduct at the department of obstetrics and gynecology at bint al huda teaching hospital in Thiqr city between the 1st of march 2012 to the 1st of march 2013 in which 80 patients aged between (20 to 37 years old) with unexplained IUGR and oligohydramnios referring to

participated in our study, all patient were interviewed about their medical, personal, obstetrical and family history. Each patient was asked to sign an informed consent before involvement in the study.

In those patients all known causes of IUGR and oligohydramnios has been excluded like pre-eclampsia, chronic medical disorders, rupture membrane, congenital anomalies of the fetus, ant phospholipid syndrome ect, by doing appropriate investigations related to each mention disorders. All selected patients were in good general health without previous history of Diabetes Mellitus or thyroid disorders or cardiac diseases. Patients with thrombocytopenia, bleeding tendencies and multiple pregnancies were excluded from the study. Baseline complete blood picture, urine examination, blood sugar, blood grouping, bleeding time, clotting time, prothrombin time, activated partial thromboplastin time were offer for all patients.

After computerized randomization, patients were divided into two groups: thromboprophylaxis group (n=40), who received aspirin (80 mg PO daily) and LMWH enoxaparin (40 mg SQ once daily) simultaneously after detection of early IUGR when BPD < 5.3 cm and oligohydramnios when AFI < 1 cm by U/S which examined by one person and repeated by another one for certainty, the gestational age was range between 22 weeks to 34 weeks for all participants in our study, the

other group (n=40) was the control group who received no treatment apart from the usual protocol that are used for management of IUGR and oligohydramnios which involve frequent follow up.

The patients were informed about the methods of subcutaneous self injection of LMWH, in the anterolateral sides of each arm and they received 500 mg supplementary calcium daily in order to reduce the risk of osteoporosis. Compliance as evidence from patients interview and marks of subcutaneous injection was excellent. Clotting tests and platelet count were performed before the start of medication, 5 days after initiation of treatment and monthly afterwards until delivery. Prenatal visit were performed for both groups every week till there has been improvement in the growth and liquor than after fortnightly till 36 weeks gestation when the treatment has been stopped or it has been interrupted if there was any premature labor or any other complications developed. Pregnancy outcome, occurrence of obstetrics complications and side effects of aspirin and LMWH in both mother and fetus (such as bleeding tendency, drugs allergy or thrombocytopenia in treatment group) were recorded during the follow up period. Fetal growth monitored by fundal height measurement and serial ultrasounds and Doppler umbilical wave flow velocity.

Data analyses were performed using SPSS for windows. Means (SD) and proportions were compared between the two groups using Student's t-test and chi square tests respectively. Between-group difference were regarded as significant when $P < 0.05$.

Result:

A total of 80 patients, 40 patients were randomized to have treatment and another 40 was the control group without treatment, the mean age of patients was 27.5 ± 2.6 in the treatment group and 28 ± 4.8 in the control group with no significant difference ($P = 0.210$), and there was also no significance difference regarding their parity, BMI, gestational age at the time of involvement (table 1). The rate of successful pregnancy was 30 (75%) and 15 (37.5%) in the treatment and control group respectively, so the thromboprophylaxis group had higher rate of live birth than control group ($P < 0.05$). In thromboprophylaxis group 5 (12.5%) patients and in the control group 15 (37.5%) patients had intrauterine fetal death during the period of follow up (table 3). There were no significant difference in the number of preterm deliveries (less than 37 weeks) between the two groups ($P = 0.789$). The most prenatal complication was preterm rupture of membrane in both group which was statistically non significant ($P > 0.05$). No maternal or fetal side effect was seen.

Discussion:

Oligohydramnios is a common complication of pregnancy, accompanied by fetal growth restriction or other related diseases. It is a major determinant of infant morbidity and mortality both in undeveloped and developing countries.

It is specially ominous to observe severe oligohydramnios in the second trimester as perinatal mortality rate is high, when amniotic fluid is absent, the perinatal mortality rate is high at (90%) ⁽¹²⁾. The lethal complication of severe oligohydramnios is a result of pulmonary hypoplasia. Currently, obstetricians are looking for some modalities of treatment such as maternal hydration, amnioinfusion, transabdominal amniocentesis prior to lobar induction but whether routine antepartum or intrapartum treatment will improve outcome remains to discover.

In our study, the term live birth was 75% in the thromboprophylaxis group while 37.5% in the control group which was with higher significance ($P < 0.05$) and this is because heparin treatment in patients with preterm oligohydramnios was generally successful but the detail mechanism need to be further studied. As we know heparin can promote blood circulation and improve placental function by decreasing platelets aggregation, increasing exogenous anticoagulant activity, inhibiting fibrin

formation and deposition, and decreasing thrombosis in the placenta, also in our study there was (12.5%) of intrauterine death in the thromboprophylaxis group compared to (37.5%) in control group which was statistically significance ($P < 0.05$) which mean that heparin is also successful in reduce perinatal mortality from IUGR.

According to previous study⁽¹³⁾ that show heparinase expression in preeclampsia and eclamptic placentas and several oligohydramnios placentas, they found that the expression of heparinase is stronger in these placentas than in normal placentas, and this was one of the reason why patients with oligohydramnios need heparin, it may be that overproductions of heparinase in placenta broke endogenous heparin and reduce blood circulation, thus reduce the glomerular filtration rate leading to reduce fetal urine and lung fluid so source of amniotic fluid decreased. Therefore, the mechanism of heparin for oligohydramnios needed further studies in multiple centers in randomized control trials. However, other measures that these women received, such as strict follow up of all women, might have affected the results because close follow up has been reported to have beneficial effect on pregnancy outcome in those women. LMWH does not cross the placenta, no fetal or neonatal complication has been reported and recent studies have confirm the safety

of LMWH therapy during pregnancy and low risk of side effect for both mother and neonate ⁽¹⁴⁾ . aspirin may improve pregnancy outcome by irreversibly blocking the action of cyclo-oxygenase in platelets, thereby inhibiting platelet thromboxane synthesis and preventing thrombosis of placental vasculature ⁽¹⁵⁾ . also studies have shown that aspirin with both anti-inflammatory and anti-coagulant effects is safe drug during pregnancy when administered at low dose (50-150 mg). And also other studies have not shown any increasing

risk of bleeding either for the mother or the fetus ⁽¹⁶⁾ . Of course further studies with larger sample size are recommended to reach a more comprehensive conclusion.

Conclusion:

Aspirin and LMWH are successful in treatment of IUGR accompanied by early onset oligohydramnios by increasing the rate of live birth with few side effects for both the mother and fetus.

Table 1: sociodemographic characteristics of the patients.

Variable	Thromb- Prphylaxis(n=40)	Control (n=40)	P value
Age	27.5(2.6)	28.3(4.8)	0.210
Parity	2.8(1.3)	3.1(1.3)	0.152
GA at enrollement	22.3(1.6)	24.2(1.4)	0.416
Previous complication	4.1(2.1)	3.9 (3.2)	0.651

*GA: gestational age.

Table2: prenatal complications in both groups.

Variable	Thromb- Prphylaxis(n=40)	Control(n=40)	P value
Preeclmpsia	2(5%)	8(20%/)	>0.05
PROM	6(15%)	8(20%)	>0.05
IUFD	5(12.5%)	15(37.5%)	<0.05

***PROM: premature rupture of membrane.**

***IUFD: intrauterine fetal death.**

Table 3: outcome of pregnancy in both groups.

Variable		Thrombo- prophylaxis(n=40)	Control (n=40)	P value
Live birth at term (37 wk)		30(75%)	15(37.5%)	<0.05
Preterm birth less than (36wk+6 days)		5(12.5%)	10(25%)	>0.05
Mode of delivery	C/S	35(87.5%)	25(62.5%)	<0.05
	NVD	5(12.5%)	15(37.5%)	<0.05

***C/S: caesarion section.**

***NVD: normal vaginal delivery.**

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تقييم فعالية الاسبرين والهيبارين منخفضة الوزن الجزيئي في المرضى الذين يعانون من تقييد النمو داخل الرحم غير المبررة يرافقه قلة السائل السلوي بداية مبكرة

نادية صدام الاسدي

الخلاصة:

المقدمة:

لوحظ هنالك دور للسيتوكينات الالتهابية وتخثر المشيمة المحلي في المرضى الذين يعانون من تقييد النمو داخل الرحم غير المبررة يرافقه قلة السائل السلوي بداية مبكرة وبما ان الاسبرين والهيبارين منخفضة الوزن الجزيئي له دور مضاد للالتهاب ومضاد لتجلط الدم لذا قمنا بتقييم فعاليتهم في علاج المرض المذكور أعلاه.

طريقة العمل:

دراسة مقارنة مستقبلية أجريت في مستشفى بنت الهدى التعليمي في محافظة ذي قار للفترة من الأول من آذار ٢٠١٢ ولغاية الأول من آذار ٢٠١٣ حيث شملت مشاركة (٨٠) امرأة تراوحت أعمارهم من (٢٠-٣٧) سنة واللواتي يعانين من تقييد النمو داخل الرحم و قلة السائل السلوي ، قسمت إلى مجموعتين، المجموعة الأولى (٤٠) مريضة استلمت علاج الاسبرين و الهيبارين والمجموعة الثانية (٤٠) مريضة هي المجموعة الضابطة والتي لم تستلم علاج فقط البروتوكول المعتاد في التعامل مع حالات تقييد النمو داخل الرحم و قلة السائل السلوي والتي تضمن المتابعة المستمرة. معدل الولادات الحية، مضاعفات الحمل والتأثيرات الجانبية للأدوية اعتبرت نتائج للدراسة

النتائج:

لوحظ انه لا يوجد فرق من ناحية العمر و عدد الأطفال ومعدل الوزن وعمر الجنين في وقت الدراسة بين المجموعتين. بينما لوحظ معدل الولادات الحية (٧٥%) للمجموعة التي أخذت العلاج و (٣٧.٥%) للمجموعة الضابطة، لهذا المجموعة التي أخذت العلاج لديها معدل ولادات حية أعلى مقارنة بالمجموعة الضابطة ($p < 0.05$). وأيضاً لوحظ معدل الولادات الميتة (١٢.٥%) للمجموعة التي أخذت العلاج (٣٧.٥%) للمجموعة الضابطة، كما أظهرت الدراسة انه لا يوجد فرق بالنسبة للولادات المبكرة ولا توجد أي مضاعفات دوائية بالنسبة للام والطفل.

الاستنتاج :

أن الاسبرين والهيبارين منخفضة الوزن الجزيئي هما دوائيين فعالين في علاج المرضى الذين يعانون من تقييد النمو داخل الرحم غير المبررة يرافقه قلة السائل السلوي بداية مبكرة من خلال زيادة معدل الولادات الحية مع تأثيرات جانبية قليلة للام والطفل.