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Management of severe oligohydramnios with antepartum transabdominal amnioinfusion

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Introduction

The amniotic fluid provides an ideal environment for fetal development and growth. It protects the fetus from trauma, and allows normal movements, which is important for musculoskeletal development. The amniotic fluid provides the fetus with a source of water, participates in the fetal metabolism, maintains a constant temperature and plays a crucial role in the development of the fetal lungs. Abnormalities of composition are much rarer than those of volume, and in most cases of abnormality of volume the composition is normal for the gestational age. The average amniotic fluid volume increases progressively from 1.5 ml at 7 weeks to 20-25 ml at 10 weeks, 630 ml at 22 weeks and 770 ml at 28 weeks of gestation. At the beginning of pregnancy, the amniotic fluid volume is a multiple of the fetal volume, but they become equal after 20 weeks. Between 29 and 37 weeks, there is only a slight change, with a peak around 34 weeks, and the amniotic fluid subsequently decreases during the pregnancy. The volume of the amniotic fluid is the resultant of the inflow and the outflow in the amniotic space. As compared with the early stages of pregnancy, much more is known about the pathways involved in this regulation during the second half of gestation, after keratinization of the fetal skin.

Oligohydramnios is believed to complicate 4-4.9% of pregnancies. Oligohydramnios has six possible major causes: 1) a severe fetal abnormality, 2) preterm premature rupture of the membranes, 3) an isolated/idiopathic form, 4) an impaired placental function leading to insufficiency, 5) a complication of multiple pregnancies, and 6) iatrogenic. There are two peaks in the incidence of oligohydramnios, between weeks 13 and 21 and between weeks 34 and 42. In the clinical practice, the amniotic fluid volume is usually estimated by ultrasonography. Besides the subjective estimation, two methods of assessment are frequently used in clinical practice: 1) the amniotic fluid index, and 2) measurement of the single deepest pocket.

In the third trimester, oligohydramnios has been reported to associated with increased level of labor induction, stillbirth, a nonreassuring fetal heart rate, iatrogenic premature delivery, meconium aspiration syndrome, admission to a neonatal intensive care unit and neonatal death. On the other hand, the association between oligohydramnios and neonatal acidosis has not been sufficiently demonstrated. Other authors have found oligohydramnios to be a significant risk factor for an adverse perinatal outcome only in the presence of

intrauterine growth retardation, while isolated oligohydramnios in the third trimester does not seem to involve a risk of perinatal morbidity.

Extreme and persistent mid-trimester oligohydramnios, prior to 22–24 weeks, before the saccular stage of lung development leads to pulmonary hypoplasia. It poses a risk of perinatal mortality as high as 80% and survivors often have to face with chronic pulmonal morbidities. Additionally, there is an increased risk of cord compression, joint contractures, skeletal anomalies, growth delay and pregnancy loss. The proper management of these cases is still a big challenge for both the obstetrician and pediatrician.

My investigation focused on the importance of oligohydramnios and the possibilities of its management. This thesis consists of three main parts:

1. Assessment of oligohydramnios, other maternal and fetal risk factors and causes of death in pregnancies complicated with intrauterine fetal death.
2. Meta-analysis of relevant publications on the treatment of oligohydramnios between 13-26 weeks of pregnancy. Expectant management, transabdominal amnioinfusion and amniopatch technique were compared especially in terms of survival, pulmonary hypoplasia and postural deformities.
3. Observational study on the outcome of transabdominal amnioinfusion in case of idiopathic oligohydramnios between 16-34 weeks in our pregnant population.

Analysis of oligohydramnios and other risk factors in cases with stillbirth through autopsy and placental examination reports

Materials and methods

We carried out a retrospective analysis on the total number of stillbirths that occurred at the Department of Obstetrics and Gynecology, University of Szeged, Hungary, between 1996 and 2010. Only cases with a gestational age of 24 weeks or more were surveyed, and also stillbirths with a birth weight of at least 500 g if the gestational age was unknown. The pregnancy characteristics and the comprehensive autopsy results were collected from the medical charts. The cause of stillbirth was determined by a consensus between the gynecologists on the basis of relevant clinical findings that can explain subsequent stillbirth and the pathologists who reported the autopsy and placental histopathological results.

Results

Overall 140 stillbirths and 29,897 births occurred during the 15-year period, representing an average stillbirth rate of 4.7 per 1000. One hundred and twenty-six of the 140 stillbirths (90.0%) occurred in singular pregnancies, and the remaining 14 (10.0%) in twin pregnancies. The median gestational age at delivery was 31 weeks (range: 24-40 weeks), whereas two postdate stillbirths were recorded. The median maternal age was 28 years (range: 18-45 years). Hypertensive disorders were present during pregnancy in 27 cases (19.3%), while diabetes occurred during pregnancy in 13 cases (9.2%). The incidences of the maternal risk factors are listed in Table 1. Regarding the fetal factors, the most common fetal finding was the intrauterine growth retardation, which was demonstrated in 67 of the 140 cases (47.8%). Oligohydramnios was diagnosed in 14 cases (10.0%) and the fetus was large for gestational age in 12 cases (8.6%). A lethal abnormality was noted in 3.6% (5/140) of the cases. The incidences of the fetal risk factors are illustrated in Table 2. It is of paramount importance that oligohydramnios was significantly associated with growth retardation: 78.6% of the fetuses with oligohydramnios were growth-retarded. No other condition was found to be associated with a low volume of the amniotic fluid. The postmortem examination revealed the cause of death in 81 cases (57.9%), while 56 cases (40.0%) remained unexplained (mean gestational age ± standard deviation (S.D.): 31.03 ± 4.29 weeks). The results of the autopsy and the histological examinations of the placenta are presented in Table 3.

Table 1. Incidence of maternal risk factors

Maternal age (year) (mean ± S.D.)	28.5 ± 6.0	
Gestational age at stillbirth (week)	31.2 ± 4.0	
Maternal risk factor	**N = 140**	
	n	**%**
Maternal obesity[a]	31	22.1
Inadequate antenatal care[b]	29	20.7
Hypertensive disorder[c]	27	19.3
Advanced maternal age (>35 years)	22	15.7
Maternal smoking	21	15.0
Gestational diabetes mellitus	10	7.1
Recurrent early pregnancy loss	7	5.0
Pregnancy after *in vitro* fertilization	6	4.3
Previous stillbirth	5	3.6
Type1 diabetes mellitus	3	2.1

[a:] Maternal obesity is defined as a body mass index (BMI) > 30 kg/m^2

[b]: Number of antenatal care visits ≤ 1

[c]: Including all grades of pre-eclampsia, pregnancy-induced hypertension and essential hypertension

Table 2. Incidence of fetal risk factors

Fetal risk factor	N = 140	
	n	%
Intrauterine growth-retarded fetus	67	47.8
Oligohydramnios	14	10.0
Large for gestational age fetus	12	8.6
Lethal congenital anomaly	5	3.6
Isoimmunization	2	1.9
Placenta previa	2	1.9
Hydramnios	1	0.9

Table 3. Causes of fetal death (autopsy and/or placental histological results)

Cause of death	N = 140	
	n	%
Placental insufficiency	38	27.1
Umbilical cord origin	21	15.0
Fetal infection	8	5.7
Lethal congenital anomaly	5	3.6
Placental abruption	5	3.6
Hydrops fetalis	4	2.9
Unexplained	56	40.0
Either autopsy or histological examination of the placenta not performed	3	2.1

Discussion

Fetal death is a sensitive obstetric care indicator and stillbirth still plays a major role in perinatal mortality. The stillbirth rate worldwide varies from 2.1 per 1000 to 40 per 1000 births, and our rate of 4.7 per 1000 is in concordance with the data obtained from other high-income regions of the world. Despite our high autopsy/placental examination rate (97.9%), the number of unexplained stillbirths was still 42.1% of the total. In other studies, the rate of stillbirths with no apparent cause varied between 23.2 and 66.2%, but the rate of unexplained

stillbirths and the distribution of cases into causes of death groups varies depending on the classification system used.

Oligohydramnios occurred in 10% of the cases and appeared to be a noteworthy factor in fetal death. This prevalence is at least double that reported in population studies. The role of a reduced amniotic fluid volume in the prediction of fetal death is still questionable. The fundamental work of Chamberlain et al. demonstrated a more than 55-fold increase in perinatal mortality if serious oligohydramnios was present. Several studies found oligohydramnios to be an independent risk factor of intrauterine fetal death. Chhabra et al. reported a perinatal mortality of 18% in a group of high-risk pregnancies with oligohydramnios. Our result seems to support the observation of Apel-Sarid et al., who found oligohydramnios to be a significant risk factor for an adverse perinatal outcome in pregnancies complicated with intrauterine growth retardation.

Treatment strategies for severe second and early third trimester oligohydramnios

Materials and methods

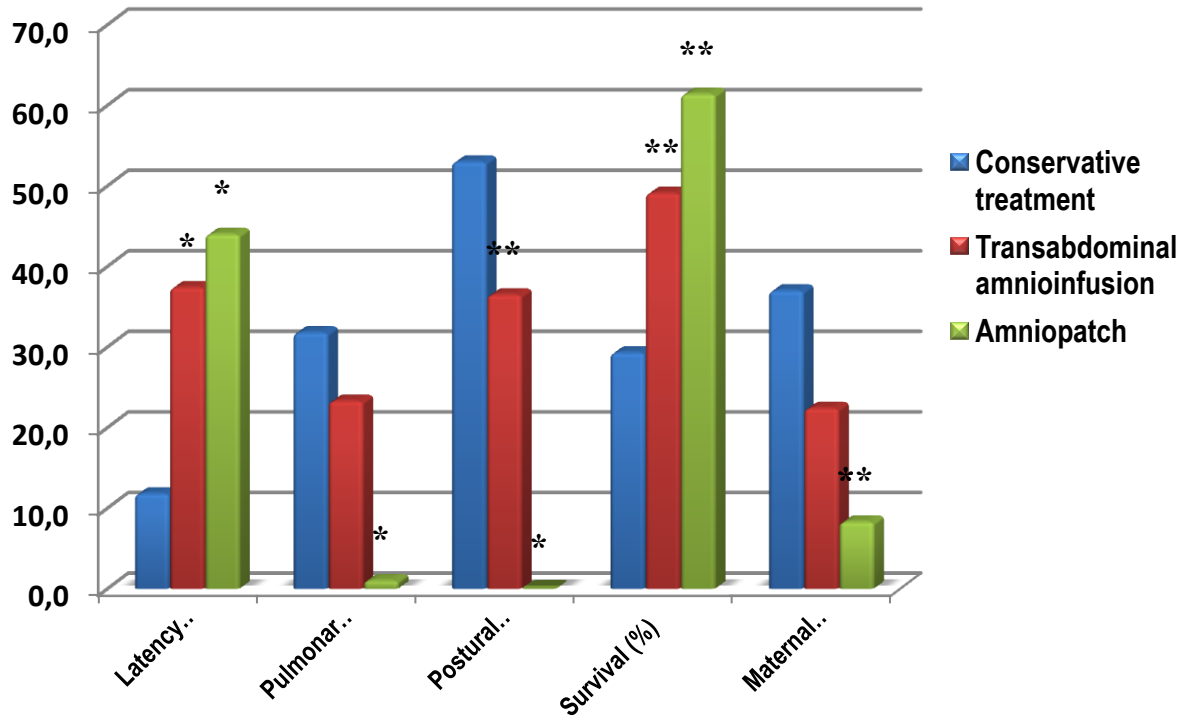
A systematic review and meta-analysis were conducted. Studies on the management of second- and early third trimester (13-26 weeks of gestation) oligohydramnios were reviewed from 2000 to 2013 in the conservative management and antepartum transabdominal amnioinfusion group, and all the reported cases with amniopatch were analyzed. In the pooled analysis $\chi 2$ test and Student's t-test were applied. Statistical significance was defined at the two-sided $p=0.05$ level.

Results

Nine studies in the amnioinfusion group, 12 studies in the amniopatch group and 7 studies in the conservative management group were analyzed. The expectant management delayed pregnancy by a mean latency of 11.8 days (range 0-163). Pulmonary hypoplasia developed in 31.8% in this group. The overall perinatal survival rate following expectant management was 29.3%, while deformation defects occured in 53%. In the amnioinfusion group the latency was significantly longer at 37.4 days ($p<0.001$). Pulmonary hypoplasia developed in 23.3%, although chronic lung diseases complicated the neonatal period in 34.8%. The overall perinatal survival was 49.1%, and the deformation defects were reduced to

36.5% ($p<0.05$) by amnioinfusion. The rate of severe maternal complications as infection or placental abruption occured in 22.4%. After amniopatch, the pregnancy was delayed by 44 days ($p<0.001$). Both pulmonary hypoplasia and chronic lung diseases were below 1%. The perinatal survival was 61.4%. Postural deformity was not recorded among amniopatch survivors. Procedure-related maternal complications were 28.2%, but serious complications as infection or placental abruption occured in 8.3% only. The main outcomes of the three management strategies presented on Figure 1.

Figure 1. Outcomes of three management strategies
in case of second- and early third trimester (13-26 weeks) oligohydramnios



*: $p<0.001$ and **: $p<0.05$ compared to conservative management

Discussion

In our study we aimed to analyze the latest perinatal results in midtrimester oligohydramnios management, since the improvement of neonatal intensive care units has an outstanding impact on perinatal outcomes. However, the prognosis of midtrimester oligohydramnios is still poor. Besides the fetal malformations, preterm premature rupture of the membranes is the most frequent cause of decreased amniotic fluid volume in this period of gestation. The traditional obstetric management includes the administration of tocolytics and antibiotics to prolong latency and steroid administration to enhance pulmonary maturity. In

the conservative treatment group we demonstrated a mean latency of only 11.8 days from rupture of membranes until delivery. The 73% of pregnancies ended within two weeks after rupture of membranes. In the majority of the cases, during this short period the fetus couldn't reach the limit of viability.

Antepartum transabdominal amnioinfusion is the method that has been addressed as a technique for the restoration of a normal amniotic fluid volume, in order to prolong gestation and to prevent fetal complications at least until pulmonary maturity is achieved. The technical equipment is similar to that used for amniocentesis; it is performed with or without local anesthesia, usually with a 20–22-gauge 150-mm amniocentesis needle, which is introduced transabdominally into the widest amnion pocket with the assistance of realtime ultrasound guidance. The infused crystalloids are 0.9% saline solution or Ringer's lactate solution at body temperature, which are both isotonic and do not induce any electrolyte imbalance in the fetus. In our analysis, we demonstrated that survival increases to 49.1% and it is a significant improvement compared to expectant management. This encouraging result can be derived from the significant increase in latency time and a slight reduction in the rate of pulmonary hypoplasia due to restored amniotic fluid volume. The extent of fluid loss after amnioinfusion has impact on the success of the treatment. If persistent oligohydramnios (deepest pocket of fluid 2 cm or less) requires serial amnioinfusion, lower neonatal survival and higher rates of pulmonary hypoplasia can be expected. In contrast with patients with ruptured membranes, serial amnioinfusion seems to be beneficial over single procedure in case of oligohydramnios with intact membranes.

The use of invasive prenatal diagnosis and fetal surgery has increased over the recent years. Iatrogenic preterm premature rupture of the membranes remains one of the most common complications. Risk of fluid leakage after a simple needle procedure is around 1.7 %, After a fetoscopic procedure, iatrogenic rupture of the membranes occurs in 5-30%, depending on factors such as trocar size and surgical duration. Use of amniopatch is accepted novel technique in order to achieve arteficial membrane sealing following iatrogenic amniotic fluid leakage. During the procedure warm isotonic saline is infused intra-amniotically under ultrasound monitoring without knowledge of the exact site of rupture of the amniotic membranes. Cross-matched allogenic platelets are infused, followed by cryoprecipitate (including clotting factors). With instillation of normal saline, the optimal (>5 cm) deepest pocket of the amniotic fluid bag is achieved. Theoretically, the platelet/cryoprecipitate plug may seal the amniotic membranous defect by artificial platelet activation and fibrin adhesion

at the site of the rupture, forming a 'white' coagulum as a plug. In our analysis, the overall perinatal survival rate was the highest (61.4%) after treatment with amniopatch. This technique is basically performed in case of iatrogen rupture of the membranes. In cases with spontaneous rupture, the amniopatch predominantly fails, usually because of infection and mostly large, poorly delineated membrane defects. This low success rate limits the use of amniopatch to the treatment of iatrogenic amniotic leakage, whereas spontaneous preterm premature rupture of the membranes is rather a therapeutic target for transabdominal amnioinfusion.

Management of severe idiopathic oligohydramnios with antepartum transabdominal amnioinfusion

Materials and methods:

We performed our study on patients presenting at the fetomaternal unit of the Department of Obstetrics and Gynaecology, University of Szeged, Hungary, with severe idiopathic oligohydramnios (amniotic fluid index <5 cm) during the period between December 2009 and January 2012. All possible cases with severe idiopathic oligohydramnios were enrolled into the study. The patients were in either the second or the third trimester, and the aim was prolongation of the gestation. Inclusion criteria were as follows: a) <34 weeks of gestation; b) a singleton pregnancy; c) no preterm premature rupture of the membranes; d) no symptoms indicative of incomplete abortion before 24 weeks of gestation; e) no active labour (<3 cm of cervical dilatation; <2 uterine contractions every 10 mins) after 24 weeks of gestation; f) no clear signs of maternal or fetal infection (maternal tachycardia >100/min, maternal temperature >38°C, maternal white blood cell count >15,000/ml, maternal C-reactive protein >20 mg/l, uterine tenderness, a foul-smelling vaginal discharge, fetal tachycardia >160 bpm); and g) no suspicion of placental abruption (uterine tenderness and "unexplained" bleeding episodes). We excluded from the study women with pregnancies complicated by lethal congenital abnormalities and women who declined after giving their informed consent. Under sterile circumstances, without sedation, a Chiba 20® 150-mm needle (Neomed Corporations, Debrecen, Hungary) was introduced transabdominally into the amniotic cavity, into the widest pocket of the amnion, under ultrasound guidance (Kretz Sonoace 8000, Voluson 730Pro). A variable volume of 37 °C saline solution (0.9% NaCl, 180–900 ml) was infused transabdominally into the amniotic cavity under continuous ultrasonographic control. After this, a fetal morphological evaluation was carried out with

ultrasonography by the same examiner. The patients were followed up weekly for repeated amniotic fluid index measurement in order to assess the need for further infusions again. Comparisons were assessed by the Kruskal-Wallis test for continuous variables. χ^2 analysis with the Yates' correction when necessary, or the Fisher exact test was used to test differences in proportions. A confidence level of $p < 0.05$ was taken to indicate statistical significance.

Results

Altogether 20 cases fulfilled the criteries for enrollment. The mean gestational age at the time of the initial amnioinfusion was 22.6 weeks (range: 16.0–33.9 weeks). The mean number of infusions was 1.5 per pregnancy. Amnioinfusion procedure was performed once in 14 pregnancies, twice in three pregnancies, three times in two pregnancies and four times in one pregnancy due to recurrent oligohydramnios. Thus, a total of 30 amnioinfusion were performed. The procedures were mostly repeated weekly in serial cases. The duration of pregnancy at the time amnioinfusion was performed was <24 weeks in 70% of the patients. Ten amnioinfusions were complicated by spontaneous abortion (50.0%). In four of these ten cases, retroamniotic filling of saline solution and floating amniotic membrane were observed immediately after the start of the procedure following introduction of the needle into the insertion site. Nine pregnancies ended in delivery. Table 4. compares the procedure-related characteristics in the two groups. One case was excluded from the statisctical analysis, because the pregnancy resulted in intrauterine fetal death in the third trimester and induction of labour was performed.

Table 4. Procedure characteristics of pregnancies with severe oligohydramnios treated with transabdominal amnioinfusion (APTA). Comparison of cases resulted in delivery and spontaneous abortion.

	Pregnancy followed by delivery (n=9)		**Procedure-related spontaneous abortion (n=10)**			
	n	%	n	%	p value	OR (95% CI)
Gestational age at first APTA (mean in weeks) (range)	25.3 (21.0-33.0)		20.0 (16.0-23.9)		n.s.	0.44 (0.21-0.92)
Latency period (days) (mean)	54.4±42.1		4.3±4.4		0.001	
Single procedure	4	44.4	10	100	n.s.	
Volume infused at first APTA (ml) (mean ± S.D.)	430.0±132.2		340.0±115.9		n.s.	
Volume infused at all APTAs (ml) (mean± S.D.)	444.1±93.6		308.9±101.1		<0.05	

Statistical comparisons were performed with the Mann-Whitney U test and the Fisher exact test for continuous and categorical variables, respectively. Latency period: interval from first infusion to abortion/delivery. APTA: antepartum transabdominal amnioinfusion; S.D.: standard deviation; n.s.: statistically not significant; OR: odds ratio; 95% CI: 95% confidence interval

The interval between the first infusion and the spontaneous abortion/delivery (latency period) was 27.6 ± 37.2 days. Serial procedures lead to delivery at a higher gestational age than the single procedures (latency period: $p = 0.002$; repeated: 69 days vs single: 10 days).

Discussion

Our present investigation focused on selected cases with no obvious reason for severe oligohydramnios. Regarding the results, the prevalence of fetal loss (55%) was unexpectedly high. This is basically the consequence of the high proportion of spontaneous abortion in the second trimester, which was mainly the result of the procedure-related rupture of the membranes (7 of 16 second trimester cases). These findings do not correlate with observations of other investigations. By our experience if the amnioinfusion is followed by rupture of the membranes within a short time period (3 days) in the second trimester, or retroamniotic filling appears, then the risk of spontaneous abortion is fairly high. The earlier the severe idiopathic oligohydramnios develops, the higher the risk of rupture of the membranes and spontaneous abortion following amnioinfusion. In our study, in the vast majority (75%) of cases the severe idiopathic oligohydramnios developed in the second trimester. If rupture does not occur in the first 3 days, then the probability of the prolongation of gestation is significantly increased, but more than one procedure is typically required (62.5%) due to the recurrence of the oligohydramnios. As compared with other studies, severe idiopathic oligohydramnios was treated with a significantly higher volume of infused fluid in our study (mean amount of fluid infused was 397.3-ml saline). Higher volume of saline infused into the amniotic cavity poses a lower risk of rupture. In other words, a higher initial amniotic fluid volume requires a lower amount of infused saline, which represents a higher probability of rupture of the membranes fairly rapidly.

Although no maternal intraprocedural complications were recorded, the rate of placental abruption in our study group is noteworthy. We experienced placental abruption in 3 pregnancies (15%), with several days after the last amnioinfusion (mean: 12.7 days; range: 7-24 days). This proportion is in line with the 9-16.7% rate reported previously in the literature. However, the transadominal amnioinfusion procedure seems not to increase the risk of this complication, since similar rate of placental abruption was found in amnioinfusion cases to

that experienced in cases without intervention (16.0 vs. 23%). This is supported by the fact, that oligohydramnios is shown to be an independent risk factor for placental abruption. If we consider the results of previous reports, the benefits of the procedure exceeds the risk of spontaneous abortion, although the decrease of amniotic fluid volume in the second trimester still poses an unfavourable prognosis.

List of publications related to the Thesis

I.

Kozinszky Z, **Pásztor N**, Vanya M, Sikovanyecz J, Pál A. Management of severe idiopathic oligohydramnios: is antepartum transabdominal amnioinfusion really a treatment option? J Matern Fetal Neonatal Med. 2013;26(4):383-7. ***IF: 1.518***

II.

Pásztor N, Keresztúri A, Kozinszky Z, Pál A. Identification of causes of stillbirth through autopsy and placental examination reports. Fetal Pediatr Pathol. 2014;33(1):49-54. ***IF: 0.580***

III.

Kozinszky Z, Sikovanyecz J, **Pásztor N**. Severe midtrimester oligohydramnios: treatment strategies. Curr Opin Obstet Gynecol. 2014;26(2):67-76. ***IF: 2.637***

IV.

Pásztor Norbert dr, Sikovanyecz János dr, Kozinszky Zoltán dr, Németh Gábor dr, Pál Attila dr. Az antepartum transzabdominális amnioinfúzió szerepe a súlyos oligohydramnion kezelésében (The role of antepartum transabdominal amnioinfusion in the management of severe oligohydramnios) [in Hungarian] Magy Nőorv L (accepted for publication)

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Blessed is the one
who does not walk in step with the wicked
or stand in the way that sinners take
or sit in the company of mockers,
but whose delight is in the law of the LORD,
and who meditates on his law day and night.
That person is like a tree planted by streams of water,
which yields its fruit in season
and whose leaf does not wither—
whatever they do prospers.

/Psalms 1:1-3/