Economic evaluation studies of obstetric interventions in high risk pregnancies
Vijgen, Sylvia

Citation for published version (APA):
Vijgen, S. M. C. (2013). Economic evaluation studies of obstetric interventions in high risk pregnancies

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Economic analysis comparing induction of labour and expectant management for intrauterine growth restriction at term (DIGITAT trial)
Abstract

Objective Pregnanecies complicated by intrauterine growth restriction (IUGR) are at increased risk for neonatal morbidity and mortality. The Dutch nationwide disproportionate intrauterine growth intervention trial at term (DIGITAT trial) showed that induction of labour and expectant monitoring were comparable with respect to composite adverse neonatal outcome and operative delivery. In this study we compare the costs of both strategies.

Study design A cost analysis was performed alongside the DIGITAT trial, which was a randomized controlled trial in which 650 women with a singleton pregnancy with suspected IUGR beyond 36 weeks of pregnancy were allocated to induction or expectant management. Resource utilization was documented by specific items in the Case Report Forms. Unit costs for clinical resources were calculated from the financial reports of participating hospitals. For primary care costs Dutch standardized prices were used. All costs are presented in Euros converted to the year 2009.

Results Antepartum expectant monitoring generated more costs, mainly due to longer antepartum maternal stays in hospital. During delivery and the postpartum stage, induction generated more direct medical costs, due to longer stay in the labour room and longer duration of neonatal high care/medium care admissions. From a health care perspective, both strategies generated comparable costs: on average €7106 per patient for the induction group (N=321) and €6995 for the expectant management group (N=329) with a cost difference of €111 (95%CI: €-1296 to €1641).

Conclusion Induction of labour and expectant monitoring in at term IUGR have comparable outcomes (N=329) with a cost difference of €111 (95%CI: €-1296 to €1641).

Introduction

Intrauterine growth restriction (IUGR) at term is a major problem for obstetricians in clinical practice, because it is associated with increased neonatal mortality and short and long term neonatal morbidity

At present there is no consensus among obstetricians on what policy to follow in pregnancies with suspected foetal growth restriction at term. Induction of labour might increase the risk of instrumental deliveries and caesarean sections, and therefore increase maternal and neonatal morbidity as well as costs. Expectant management on the other hand might increase the risk of perinatal complications, including stillbirth.

Since evidence on this point was lacking, we recently performed a randomized clinical trial on the subject, named the Disproportionate Intrauterine Growth Intervention Trial at Term (DIGITAT; number ISRCTN10363217). In this 650 patient study, the composite adverse neonatal outcomes and caesarean sections were comparable in both groups.

In the expectant group babies were delivered on average 10 days later and weighted 130g more as compared to the induction group. Overall, in women with suspected IUGR at term no important differences were found between induction of labour and expectant monitoring concerning immediate adverse neonatal outcome or operative delivery rate, although significantly more neonates from the induction group were admitted to high or medium levels of care. It is unclear whether these strategies differ in terms of costs generated by health care utilization. At present, evidence on costs and cost-effectiveness of management of women with suspected IUGR at term is limited.

This study reports the economic evaluation that we performed alongside the DIGITAT trial, in which induction of labour and expectant monitoring were compared in pregnancies complicated by suspected intrauterine growth restriction beyond 36 weeks of gestation.

Materials and Methods

Full details of the DIGITAT trial were reported previously. The trial was approved by the Institutional Review Board of the University of Leiden and had local approval from Boards of the other participating hospitals. The trial has been registered in the clinical trial register as ISRCTN10363217.

In short, the study was a multicentre randomized controlled clinical trial in obstetric departments of 8 academic and 44 non-academic hospitals in The Netherlands. Women diagnosed with suspected IUGR beyond 36 weeks of pregnancy with a singleton foetus in cephalic presentation were allocated to either induction of labour or expectant monitoring. Suspected IUGR was defined as a foetal abdominal circumference (FAC) below the 10th percentile, or an estimated foetal weight (EFW) below the 10th percentile, or a flattening of the FAC curve by ultrasound.

In the induction group, labour was induced within 48 h after randomization, according to local protocol. In the expectant group, patients were monitored by local protocol until the onset of spontaneous delivery, with daily foetal movement counts, and at least twice weekly foetal heart rate tracings and weekly ultrasound examination. If there were signs of sub-optimality in any of these recordings,
induction of labour was the treatment of choice. Maternal monitoring consisted of frequent blood pressure measurements, assessment of proteinuria and laboratory tests of liver and kidney function and full blood count, all at the discretion of the attending obstetricians. Monitoring could take place in an outpatient setting or during admission to the hospital.

All patients who declined randomization but gave authorization for the use of their medical data were registered as non-participants. Identical data were collected prospectively and entered into the trial database. The primary outcome in this trial was a composite measure of adverse neonatal outcome, defined as death before hospital discharge, 5-min Apgar score < 7, umbilical artery pH < 7.05, or admission to the neonatal intensive care.

Analysis of the clinical endpoints showed comparable neonatal outcomes between both groups, the prevalence of composite adverse neonatal outcome was 17 (5.3%) for the induction group versus 20 (6.1%) in the expectant monitoring group; difference – 0.8% (95% CI: – 4.3% to 3.2%). There was no perinatal mortality in the trial. The numbers of caesarean sections (respectively 45 (14.0%) versus 45 (13.7%); difference 0.3% (95% CI: – 5.0% to 5.6%)) were comparable as well.7

A cost analysis was performed alongside the trial. We used a health care perspective, in which only medical costs are included, with a time horizon until hospital discharge. Thereby, by documenting details on utilization of health care resources, we provide insight in the clinical origins of costs associated with management of these high-risk pregnancies.

As both strategies were comparable in terms of health outcomes, we performed a cost-minimization analysis in which only the costs of both strategies were compared.8 We differentiated three phases of the clinical process in which costs arise: antepartum costs (from the moment of randomization until childbirth), costs related to the delivery, and postpartum costs (from the moment of childbirth until hospital discharge). When in economic evaluations cost and/or effect are incurred at substantially different times, we need to adjust for time preference (discounting). Discounting refers to our differential valuation of a good or service, depending upon when the good or service is consumed.9 Discounting should be considered necessary only in economic evaluations with a time horizon over 1 year. Therefore no discounting was applied in this study because all costs occurred within 1 year.

Resource use during the admission period was documented in the Case Report Form (CRF). The following resource items were collected: maternal and neonatal admissions, method of delivery, outpatient visits, medication, maternal laboratory tests, cardiotocograms (CTGs) and foetal ultrasounds. Maternal admissions were differentiated into three levels of care (intensive, medium, or ward). Neonatal admissions were divided into four levels of care (intensive, high, medium, or ward). Neonatal admissions on maternal ward were not included in our analyses because we assumed these were already included in the maternal ward costs.

The time in the labour room was calculated as the time from admission to labour room to time of birth plus 1 h extra for recovery care. Assuming that induction of labour takes place inside the labour room it was hypothesized that stays in the labour room will be longer in the induction group due to time needed for induction. In cases where a caesarean section was performed, use of the operation room (in hours) was estimated as well.
Unit cost estimates were based on several sources: top-down calculations provided by the financial departments in one participating academic and one participating general hospital (for maternal and neonatal admissions to ward, medical care, obstetric high care, NICU and neonatal monitoring); bottom-up calculation (1 h use of the labour room and operating theatre), Dutch standardized prices (visits to primary and paramedical health care providers and outpatient visits), and market prices (medication). In Table 1 unit costs together with valuation methods and sources are presented. All unit costs were expressed in 2009 Euros using the consumer pricing index.

Group differences in resource use were tested by using the nonparametric Mann-Whitney U test, because such data are generally not normally distributed. Resource use per patient was multiplied by unit costs, and total costs per patient were estimated. Mean total costs per patient as well as median costs were estimated, and differences in total costs between study groups are tested using the non-parametric Mann-Whitney test. Differences in mean costs and 95% confidence intervals were determined by bootstrapping.

Seven univariate sensitivity analyses were performed to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis. Several assumptions were made in estimating labour and operation room costs by using a bottom-up method, such as time spent in labour room and/or operation room by obstetricians and gynaecologists. In the first sensitivity analysis some variations of these assumptions were made to find out their impact on the final results (model 1).

Because most cost differences were expected ante partum due to longer maternal hospital stays in the expectant group, we wanted to find out the impact of lower valuation of the ante partum admissions by assuming several other monitoring strategies: day care instead of inpatient care (model 2), outpatient visits plus CTGs instead of inpatient care (model 3) and home care instead of inpatient care (model 4).

In our base case analysis we included no costs for the neonatal ward admissions because we assumed this was covered by the maternal ward admissions. In model 5 we priced neonatal ward admissions to check its impact. Finally the impact of using lower or higher unit costs during all the phases was studied in model 6 and 7.

The DIGITAT study group performed a subgroup analysis in which they compared induction versus expectant management in women randomized before 38 weeks, from 38 till 40 weeks and after 40 weeks for three outcomes (neonatal admissions, positive MAIN score and composite adverse outcome).

The only difference was a higher percentage of neonatal admissions after induction before 38 weeks gestational age; 125 (61%) admissions vs. 92 (44%) after expectant management, difference 16% (95% CI: 6.7- 26%), p=0.001. Therefore a cost difference could be expected before 38 weeks’ gestational age and we performed a subgroup analysis to assess cost effect in patients with gestational age below 38 weeks.

Statistical and simulation analyses were performed using SPSS software (version 16.0) and Microsoft Excel.

Results

Between November 2004 and November 2008, we approached 1116 women, of whom 650 were randomized to induction (N = 321) or expectant management (N = 329), 452 declined randomisation and 14 refused any use of identifiable data.

Average volumes of resource utilization, total costs in each study group as well as average costs per patient are presented in Table 2. During the ante partum phase from moment of randomization until start of delivery, maternal admissions were longer in the expectant monitoring group, 2.8 versus 8.2 days for medium care (p < 0.05) and 2.2 versus 4.7 days on maternal ward (p < 0.001). More outpatient CTGs (2.1 versus 4.8, p < 0.001), ultrasounds (1.3 versus 2.1, p < 0.001), scheduled outpatient visits (1.9 versus 4.4, p < 0.001), unscheduled outpatient visits (1.3 versus 1.6, p < 0.001) and maternal assessments (5.4 versus 9.9, p < 0.001) occurred in the expectant monitoring group. Admission because of labour was somewhat longer in the induction group (1.8 days versus 1.4 days, p < 0.001). The duration of admission in the labour room and/or operating theatre was also longer for the induced patients in cases of spontaneous delivery (15.4 versus 8.3 h, p < 0.001), in cases of vacuum or forceps extractions (25 versus 11 h, p < 0.05) and in caesarean deliveries (18.3 versus 11.9 h, p < 0.05). From childbirth until hospital discharge no significant differences appeared in the duration of maternal and neonatal admissions. As can be seen from Table 2, however, more neonates in the induction group were admitted to medium care wards compared to the expectant monitoring group (44% versus 31%).

A summary of the mean and median costs per patient is provided in Table 3. In the antepartum period mean costs per patient appeared to be higher in the expectant monitoring group (difference - €931). On the other hand, during delivery induction of labour generated more costs than expectant management (difference €807), mainly because induction required a longer stay in the labour room and/or operation room by obstetricians and gynaecologists. In the first sensitivity analysis some variations of these assumptions were made to find out their impact on the final results (model 1).

Seven univariate sensitivity analyses were performed to explore the impact of different assumptions and alternative unit-cost estimates on the results of the costs analysis. Several assumptions were made in estimating labour and operation room costs by using a bottom-up method, such as time spent in labour room and/or operation room by obstetricians and gynaecologists. In the first sensitivity analysis some variations of these assumptions were made to find out their impact on the final results (model 1).

Because most cost differences were expected ante partum due to longer maternal hospital stays in the expectant group, we wanted to find out the impact of lower valuation of the ante partum admissions by assuming several other monitoring strategies: day care instead of inpatient care (model 2), outpatient visits plus CTGs instead of inpatient care (model 3) and home care instead of inpatient care (model 4).

In our base case analysis we included no costs for the neonatal ward admissions because we assumed this was covered by the maternal ward admissions. In model 5 we priced neonatal ward admissions to check its impact. Finally the impact of using lower or higher unit costs during all the phases was studied in model 6 and 7.

The DIGITAT study group performed a subgroup analysis in which they compared induction versus expectant management in women randomized before 38 weeks, from 38 till 40 weeks and after 40 weeks for three outcomes (neonatal admissions, positive MAIN score and composite adverse outcome).

The only difference was a higher percentage of neonatal admissions after induction before 38 weeks gestational age; 125 (61%) admissions vs. 92 (44%) after expectant management, difference 16% (95% CI: 6.7- 26%), p=0.001. Therefore a cost difference could be expected before 38 weeks’ gestational age and we performed a subgroup analysis to assess cost effect in patients with gestational age below 38 weeks.

Statistical and simulation analyses were performed using SPSS software (version 16.0) and Microsoft Excel.
### Table 2: Resource use, mean costs per patient and total costs (2009 Euros)

<table>
<thead>
<tr>
<th></th>
<th>Induction (N = 321)</th>
<th>Expectant management (N = 329)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% patients using care</td>
<td>Mean volume*</td>
</tr>
<tr>
<td><strong>Maternal admission MC</strong></td>
<td>Days 3%</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Maternal admission ward</strong></td>
<td>Days 24%</td>
<td>2.2</td>
</tr>
<tr>
<td><strong>Home care</strong></td>
<td>Days 3%</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>Outpatient CTGs</strong></td>
<td>Procedure 20%</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>CTGs during admission</strong></td>
<td>Procedure 98%</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Ultrasound</strong></td>
<td>Procedure 12%</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Scheduled outpatient visits</strong></td>
<td>Visit 21%</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Unscheduled outpatient visits</strong></td>
<td>Visit 4%</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Maternal assessments</strong></td>
<td>Procedure 83%</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Laboratorium tests</strong></td>
<td>Test 67%</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Total antepartum</strong></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Admission because of labour</strong></td>
<td>Day 90%</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Induction PGE gel</strong></td>
<td>Gift 52%</td>
<td>1.9</td>
</tr>
<tr>
<td><strong>Induction PGE tablets</strong></td>
<td>Gift 8%</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Amniotomy and oxytocin</strong></td>
<td>Procedure 24%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Medication during labour</strong></td>
<td>Unit 51%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Spontaneous route of delivery</strong></td>
<td>Hours 78%</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>Instrumental delivery</strong></td>
<td>Hours 8%</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Caesarean delivery</strong></td>
<td>Hours 14%</td>
<td>18.3</td>
</tr>
<tr>
<td><strong>Episiotomy</strong></td>
<td>Procedure 21%</td>
<td>-</td>
</tr>
</tbody>
</table>

* of patients using care  # medication costs are an summation of several medications, therefore no unit and mean volume is given
In the subgroup analysis we divided the patients in two groups according to gestational age at randomisation, before 38 weeks and a gestational age of 38 weeks and later. In the group before 38 weeks of gestational age, induction of labour appeared to generate significantly more costs per woman than expectant monitoring. From 38 weeks’ gestational age onwards total costs per woman in the induction group (N = 129) were €6248 versus €6105 in the expectant monitoring group (N = 193), the cost difference was €1409 (95% CI: 665 - 2965). Before 38 weeks of gestational age, induction of labour appeared to generate significantly less costs per woman than expectant monitoring. Costs of over the different phases in each strategy showed higher antepartum costs (due to longer maternal admissions) in the expectant group and higher delivery costs (due to the induction itself) in the induction group. Costs due to postpartum maternal and neonatal admissions were comparable between both groups. This adds to equivalent foetal and maternal outcomes as well as quality of life, indicating that both approaches are both acceptable management strategies.

With this study we further aimed to define the best strategy in at term IUGR by analysing costs generated by induction compared to expectant management, since primary neonatal and delivery outcomes, as well as more detailed neonatal morbidity and maternal quality of life were comparable between the two strategies. The antenatal costs of expectant management in IUGR were higher due to higher consumption of medical care by monitoring mother and child, but in exchange the induction group babies had a higher medical consumption after birth, mainly due to neonatal hospital admissions. In the expectant monitoring group, both mother and child were strictly monitored, until either labour was induced because of foetal or maternal deterioration or spontaneous delivery started. As a consequence, this imposed higher resource use antenatal in the expectant group due to more monitoring of mother and child. In the induction group higher resource use after birth was observed, as more children were admitted to intermediate levels of care after induction, mainly due to lower gestational age and related birth weight at delivery. From the subgroup analysis it can be concluded that before 38 weeks of gestational age induction of labour appears to generate significantly more costs per woman than expectant monitoring and from 38 weeks of pregnancy onwards induction of labour appears to generate significantly less costs per woman than expectant monitoring. Since costs are not higher after expectant management, postponing delivery beyond 38 weeks gestation for as long as neonatal condition is reassuring is reasonable.

### Table 4: Sensitivity analyses results

<table>
<thead>
<tr>
<th>Model</th>
<th>Description alternative analyses</th>
<th>Induction (N = 321)</th>
<th>Expectant management (N = 329)</th>
<th>Differential mean cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (IQR)</td>
<td>Mean (IQR)</td>
<td>(95% CI)#</td>
</tr>
<tr>
<td>Total antepartum</td>
<td>443 (218-573)</td>
<td>1374 (824-1694)</td>
<td>-931</td>
<td></td>
</tr>
<tr>
<td>Total delivery</td>
<td>2077 (1399-2785)</td>
<td>1270 (949-1478)</td>
<td>807</td>
<td></td>
</tr>
<tr>
<td>Total postpartum</td>
<td>4586 (1914-5136)</td>
<td>4351 (1264-4271)</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>Total costs</td>
<td>7106 (4680-8510)</td>
<td>6995 (3554-7569)</td>
<td>111 (-1296 - 1641)</td>
<td></td>
</tr>
</tbody>
</table>

*Induction minus expectant management
# non-parametric confidence interval based on 1000 bootstrap replications

Table 4 shows the results of the sensitivity analyses. If we increased the labour and operation room costs from €615 to €115 and from €140 to €224 per hour, this increased mean costs in both groups and the difference increased to €347, and induction remains the most expensive strategy (model 1). Replacing antepartum inpatient care by other monitoring strategies (model 2-4) decreased the mean costs per patient in both groups, but induction remained the most expensive strategy. Including neonatal ward admissions (model 5) increased mean costs per patient in both groups, and the difference increased a little. We also estimated costs by using higher and lower unit prices for hospital stay. If we only used the unit costs from the academic centre, the mean costs per patient in both groups increased and the difference decreased to €50 (model 6). If we only used the unit costs from the general hospital, the mean costs per patient decreased, and the difference between groups decreased to –€51 (model 7).

### Comments

In this study we estimated the costs of pregnant women with a diagnosis of IUGR at term who were randomized for labour induction or expectant monitoring, using the data of the DIGITAT trial. The trial did not detect differences in maternal or neonatal outcomes or in operative delivery rates, so the economic evaluation was set up as a cost-minimization analysis. We found comparable costs after induction of labour and expectant management in women with suspected IUGR at term. Within a study horizon from moment of randomization until postpartum hospital discharge, induction of labour and expectant management resulted in comparable medical costs per patient. Unsurprisingly, the distribution of costs over the different phases in each strategy showed higher antepartum costs (due to longer maternal admissions) in the expectant group and higher delivery costs (due to the induction itself) in the induction group. Costs due to postpartum maternal and neonatal admissions were comparable between both groups. This adds to equivalent foetal and maternal outcomes as well as quality of life, indicating that both approaches are both acceptable management strategies.
admissions. Beyond 38 weeks, however, there is no evident benefit, neither in medical outcomes nor in costs, in further postponing delivery.

To our knowledge this is the first economic evaluation that prospectively compared these strategies in this patient population. We used trial-based data that were collected prospectively.

In earlier studies we reported comparable neonatal and maternal outcomes after labour induction and expectant management in at term IUGR. The same applies to more detailed neonatal morbidity. A quality of life study alongside the DIGITAT trial was performed by Bijlenga et al. on behalf of the DIGITAT study group. In this study health related quality of life was measured in 361 randomized women, 6 weeks and 6 months after childbirth, using validated questionnaires. From the results it could be concluded that in pregnancies complicated by IUGR beyond 36 weeks, induction of labour does not affect the long-term maternal quality of life.

The equipoise in antenatal and postnatal costs in the DIGITAT trial was not found in the cost-analysis of a comparable RCT, that compared induction to expectant management in women with gestational hypertension or mild pre-eclampsia at term. In that study induction of labour was less costly than expectant monitoring because of differences in resource use in the ante partum period. Because more than 50 hospitals from all over the Netherlands, teaching as well as non-teaching, participated in the DIGITAT trial, the study population was representative of the Dutch population. Women who declined randomization, however, were older, slimmer, higher educated and smoked less. In a comparison between participants and non-participants (unpublished data), we found a trend towards worse neonatal outcomes and higher operative delivery rates among non-participants. From our cost analysis it can be concluded that this finding not translates into higher costs in this group, because the costs were comparable between randomized and non-randomized patients.

Our analysis focused on a short-term time horizon and was performed from a health care perspective. The advantage of that is the use of direct clinical trial data for both costs and effects.

Because reliable follow-up data were lacking in this economic analysis we decided only to focus on the short-term medical costs. Because growth restriction is associated with a less favourable (neuro) developmental outcome, we also investigated the outcome of children randomized during DIGITAT after 2 years. As that follow-up indicated no differences in child behaviour at 2 years between induction and expectant management, we think it is not necessary to include long term and societal costs for the children in our economic analysis.

Strengths of our study are the use of trial-based data for the economic analysis, and exactly the same patients were studied as for the clinical analysis. Extrapolating the data to the general Dutch patient population is valid because of the large number and diversity of the participating hospitals. Because the trial-based economic analysis was performed within the Dutch health care system and specific Dutch unit costs were used, these results cannot automatically be translated to other settings. On the other hand we do not expect any changing conclusions if unit costs are higher or lower in other settings.

Induction of labour and expectant monitoring in pregnant women with IUGR at term have comparable outcomes immediately after birth in terms of obstetrical outcomes, maternal quality of life and costs. Costs are lower, however, in the expectant monitoring group before 38 weeks of gestation and costs are lower in the induction of labour group after 38 weeks of gestation. So if induction of labour is considered in order to pre-empt possible stillbirth in suspected IUGR, it is reasonable to delay until 38 weeks, provided there is watchful monitoring.
Reference list