IHE Report

Assistive Reproductive Technologies: a Literature Review and Database Analysis

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Assistive Reproductive Technologies: a Literature Review and Database Analysis

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Executive Summary

Objectives

This report examines the impact of multiple pregnancies and Assistive Reproductive Technologies on health resources in Alberta by addressing the following questions:

1. Is there economic evidence that assistive reproductive technologies increase health services costs?
2. Is reducing the number of embryos transferred per in-vitro fertilization cycle cost effective?
3. Does reducing multiple embryo transfers per in-vitro fertilization cycle or patient reimbursement for in-vitro fertilization procedures reduce health services costs?
4. What is the cost impact of multiple pregnancies on health services costs in Alberta?
5. What is the potential cost savings to the Alberta health system by reducing the number of multiple pregnancies resulting from assistive reproductive technologies to single pregnancies?

Questions 1 thru 3 were answered by reviewing evidence from the published literature. Questions 4 thru 5 by were answered by analyzing available Alberta Health and Wellness administrative cost data.

Literature Search and Review - Objectives 1 - 3

Multiple pregnancies increase the risk of early delivery (i.e. prematurity) and low birth weight. Babies who are born with low birth weight are at increased risk of health complications which cause increased health services costs. Assistive reproductive technologies and in-vitro fertilization in particular, are associated with multiple pregnancies and therefore contribute to increasing health services costs. The literature suggests that reducing the number of embryos transferred per in-vitro fertilization cycle to a single embryo reduces the number of multiple births resulting in better health outcomes for the baby and lower health services costs.

The evidence shows that transferring one embryo is less costly than transferring two embryos per in-vitro fertilization cycle. However, transferring one embryo may also be less effective at producing a live birth depending on a woman's age. In women younger than 37, transferring one embryo is as effective as transferring two embryos. But in women older than 37, transferring one embryo is less effective than transferring two embryos. Therefore, in women older than 37, more single embryo transfer in-vitro fertilization cycles are required to achieve comparable birth rates as transferring two embryos.

The evidence also indicates that reimbursing in-vitro fertilization procedures that transfer fewer embryos may decrease the multiple birth rate and health services costs. However, patient reimbursement was associated with doubling the use of in-vitro fertilization services and a 16% to 60% increase in the number of single embryo transfer cycles conducted.

Analyses of Hospital and Physician Cost Data in Alberta - Objectives 4 - 5

Analysis of data on hospital and physician costs for infants (born between April 1, 2004 and March 31, 2005 and followed for one year) and their mothers (from pregnancy to 3 months after birth) showed the average cost of twins and higher order multiples that were low birth weight were six ($14,253 vs. $2425) and eight times ($19,435 vs. $2425) higher than a single infant that was normal birth weight. The data also showed twins and higher order multiples were respectively, 49% and 95% predictive of being born low birth weight in Alberta. This is an important finding because assistive reproductive technologies are associated with multiple pregnancies.

According to the literature, 35% of twins and 77% of higher order multiple births are produced by assistive reproductive technologies. If this is applied to Alberta, the additional health services costs generated by assistive reproductive technologies in Alberta was approximately $5.8 million dollars, which represents close to 40% of the total health services costs for twins and higher order multiples in the province. Alternatively, if all of the twins and higher order multiples produced by assistive reproductive technologies were single births the cost savings would be approximately $3.6 million. However, a greater number of single embryo transfer cycles are required to achieve equivalent birth rates as transferring two embryos. Therefore, cost savings associated with reducing the number of embryos transferred per in-vitro fertilization cycle would be offset by the increased number of single embryo transfer cycles required to generate acceptable single birth rates and health outcomes.

Conclusions

Based on the evidence examined in this report, multiple embryo transfer IVF generates more twins and higher order multiples that are at increased risk for short and long term health complications and greater health services costs. Reducing the number of embryos transferred per in-vitro fertilization cycle is associated with reducing the number of multiple births and reducing health services costs. In Alberta, health services costs associated with twins and higher order multiples from assisted reproductive technologies was estimated at $5.8 million with a potential cost savings of $3.6 million had all twins and higher order multiples been single births. However, a greater number of single embryo transfer cycles may be required to produce equivalent results as transferring more than one embryo per in-vitro fertilization cycle. Consequently, if single embryo transfer in-vitro fertilization were to be publicly funded, cost savings in health service utilization from reduced multiple pregnancies and births would be offset by the number of additional single embryo transfer cycles needed to produce acceptable birth rates and health outcomes.

List of Acronyms

AHW	Alberta Health and Wellness
ARTs	assistive reproductive technologies
CEA	cost effectiveness analysis
CIHI	Canadian Institute for Health Information
CMG	case mix group
DAM	decision analytic modelling
DET	double embryo transfer
HOM	higher order multiples
HRQL	health related quality of life
ICSI	intracytoplasmic sperm injection
IUI	intra uterine insemination
IVF	in-vitro fertilization
ICER	incremental cost effectiveness ratio
LBW	low birth weight
NBW	normal birth weight
PGD	pre implantable genetic diagnoses
RIW	resource intensity weight
SD	standard deviation
SET	single embryo transfer

Table of Contents

Appendices

Figures and Tables:

Background to Technology Review

Assisted Reproductive Technologies (ARTs) are therapies used to treat infertility. These treatments include pharmacological stimulation of ovaries, intra uterine insemination (IUI), in-vitro fertilization (IVF), and IVF with intracytoplasmatic sperm injection (ICSI). ARTs (IVF in particular) are linked to generating a disproportionate number of multiple births because multiple embryos are fertilized to promote the probability of achieving a live birth. However, because the risk of maternal and fetal complications are two to three times greater in twin and HOM pregnancies compared to singletons, ARTs are associated with increased health services costs.[1]

Consequently, there is greater pressure being placed on fertility clinics to transfer fewer embryos. In 2001, the International Federation of Fertility Societies reported that 37 out of 39 member countries had passed national legislation or guidelines addressing the number of transferred embryos. Their concern is that if ARTs are publicly funded, payers will not only be responsible for costs of ARTs procedures themselves (particularly IVF) but also costs associated with preterm/multiple births and perinatal complications.[2] It has also been suggested that the primary objective of ARTs procedures be changed to the production of a healthy singleton baby rather than the previous definition of a successful live birth.[3]

Findings from the Canadian expert meeting on ARTs and multiple gestations indicate that due to fetal complications and premature birth, multiple births are associated with higher mortality.[4] For premature born survivors, the outcome with the greatest lifelong impact is cerebral palsy. Twins and triplets are five times (9.7% vs 1.9%) and 17 times (32.3% vs 1.9%) more likely to develop cerebral palsy than singletons. The authors report that the Infertility Association of Canada projects that full funding of IVF will increase demand for IVF services but will also result in decreasing the number of multiple gestations and births. In Ontario, for example, they estimate the total number of low birth weight babies to decrease by 1398 births leading to reduced costs of $65 million Canadian (includes both hospital and disability costs). The expert panel advocated funding for single embryo transfer and that the goal of ARTs should be the delivery of a single healthy infant.

Initial Request for Technology Review

The Alberta Perinatal Health Program submitted a proposal to the Alberta Health Technologies Decision Process to formally review ARTs. The proposal stated two primary benefits that would result from publicly funding ARTs. First, it would reduce the number of multiple gestations because, due to financial pressure, patients insist on multiple embryo transfers to maximize their chances of pregnancy. This, in turn, would minimize low birth weight (LBW) infants (resulting from preterm birth and restricted intrauterine growth) resulting in savings to health service resources.[5] If publicly funded, Alberta could also consider mandating the number of embryos transferred per IVF cycle.[5]

Second, the proposal supported publicly funding pre-implantable genetic diagnoses (PGD). PGD detects various genetic disorders (e.g. cystic fibrosis and Huntington's disease) carried by embryos and it would be conducted prior to the placement of the embryo(s) in the uterus. Implanting embryos absent of genetic defects would reduce long term costs by minimizing births of infants with genetic disorders.[5]

Report Objectives

This report addresses the following questions:

1. Is there economic evidence indicating that ARTs related procedures (e.g. multiple embryo transfer) are associated with increasing health services costs?
2. Is there evidence that reducing the number of embryos transferred per IVF cycle is cost effective?
3. Does reducing multiple embryo transfers per IVF cycle or patient reimbursement for ARTs procedures reduce health services costs?
4. What is the cost impact of multiple and LBW babies on health service utilization and costs in Alberta?
5. What is the potential cost savings to the Alberta health system by reducing ARTs twins and higher order multiples (HOM) pregnancies to singleton pregnancies?

The IHE was requested to address Questions 1 thru 3 by reviewing evidence from the published literature and to address Questions 4 thru 5 by analyzing available AHW administrative cost data.

Section 1: Review of Economic Studies

Search Strategy

Selected databases (see Appendix A for detailed search strategy were searched) in January 2008 for economic and policy information related to ARTs. For economic information, MEDLINE® (along with PubMed for the in-process records), EMBASE®, and Web of Science were searched, along with the Cochrane Database of Systematic Reviews (CDSR) and the Centre for Reviews and Dissemination Databases (DARE, NHS EED, and HTA). For policy information the search was limited to MEDLINE® and EMBASE® as they were judged to be the most relevant databases for the topic.

Selection Criteria

The search was limited to human and English language publications. The inclusion/exclusion criteria for retrieval and review of identified articles are listed below:

Inclusion Criteria

1. Studies investigate the economic, health service utilization or cost impact of ARTs on the health system.
2. Studies investigate the economic, health service utilization or cost impact of limiting embryo transfers.
3. Studies investigating the impact of publicly funding ARTs on multiple birth rates.

Exclusion Criteria

1. Opinion papers. For example, opinions or letters to the editor.
2. Non-English publications.

Quality Assessment Criteria

An informal quality assessment of economic studies was conducted using criteria adapted from Drummond et al.[4] The purpose of providing a quality assessment of economic studies in this report is to explicitly identify the components included and excluded in the studies and to provide a general assessment of the quality of the economic studies reviewed.

Search Results

There were 811 published documents identified from the literature search (see Appendix A for the search strategy, study selection, and data extraction). After reviewing their titles and abstracts, 110 studies were retrieved for further evaluation. Of the 110 studies, 18 met the final inclusion/exclusion criteria. Seven studies were related to the association between ARTs and increased health services costs and eleven were related to reducing the number of embryo transfers.

Evidence from Published Literature

Cost impact of ARTs on the health care system

Koivurova et al.[6] conducted a retrospective observational study comparing post-neonatal hospital costs between IVF/ICSI children and matched controls for singleton, twin, triplet, and quadruplet births (refer to Appendix B). Data was collected from the Finnish Hospital Discharge Register and for each child in the study included cost data from birth until 7 years of age. The costing was conducted from a payer's perspective and costs were expressed in 2004 Euros. Results indicate that compared to controls, IVF children had a significantly higher number of admissions to hospital on average (1.76 vs. 1.07) and a longer average length of stay (4.31 vs. 1.07). Costs of IVF children were 2.6 times greater than controls (€205.8 vs. €79.6 per child). However, the higher costs associated with IVF children were driven by comparisons between singleton births (i.e. IVF singleton vs. natural singleton). No statistically significant findings were found between IVF twin births and control twin births. In fact, IVF twin births had lower costs than their matched controls. Limitations with the study were that it did not include other relevant costs (e.g. ambulatory care and primary care utilization including physician visit costs), lack of sensitivity analysis, and did not indicate whether they used discounting to standardized costs to 2004. These results suggest that ARTs singletons are associated with higher hospital costs than naturally conceived singletons.

Chambers et al.[7] conducted a retrospective observational study comparing average inpatient hospital costs between ARTs and non-ARTs singletons, twins, and HOMs of both infants and mothers. Specifically, cost comparisons were made between ART singletons, twins, and HOMs with non-ART counterparts and between ART singletons, twins, and HOMs. The ART study population was derived from the Australian and New Zealand Assisted Reproductive Database which collects information on all ARTs treatment cycles, including perinatal outcomes in Australia and New Zealand (5005 mothers who gave birth to 5886 live born infants conceived following ARTs in 2003). The non-ART population was sourced from the Australian National Perinatal data collection which is a cross sectional database of all births in Australia including perinatal outcomes (250,254 mothers who gave birth to 254,425 live born infants conceived naturally in 2003). Cost data was derived from the National Hospital Morbidity Database of women who gave birth in Australia in 2003 and is expressed in 2003 Australian dollars converted to Euros. The costing was conducted from a payer's perspective. Results indicate that ARTs infants were 4.4 times more likely to be of LBW (< 2500g) and five times more likely to be of very LBW (< 1500g) compared to non-ARTs infants. Compared to non-ARTs infants, the inpatient costs were €1330 higher for ARTs infants (€2832 vs. €1502). For mothers, maternal costs for ARTs singletons, twins, and HOM were 11%, 6%, and 8% higher than their non-ARTs counterparts respectively with overall 23% higher birth admissions cost (€3321 vs. €2708). The overall cost of all ARTs birth episodes regardless of plurality was 57% higher than non-ARTs birth episodes. When comparing plurality within ARTs birth episodes, twin (€13,890) and HOM (€54,294) costs were three and 11 times higher than singletons (€4818). The authors report that approximately €9.2 million could be saved in birth admissions alone if ARTs multiples had been singleton births. The authors concluded that the results highlight the need for policies supporting single embryo transfer. Strengths of the study were that it conducted a sensitivity analysis and a thorough costing analysis. Limitations of the study were that it only focused on inpatient costs (e.g. mothers of twins and HOM may utilize greater ambulatory and primary care services). Nevertheless, the study provides a direct link between ARTs related births and increased costs to the health care system.

Ledger et al.[8] used a decision analytic model (DAM) to compare maternal and neonatal costs of IVF multiple pregnancies and IVF singleton pregnancies. Data was collected from the United Kingdom national statistics database between April 1, 2000 and March 31, 2001 and included total number of births resulting from IVF treatment and cost data from pregnancy until one year of age. The IVF population consisted of 4621 singletons, 1579 twins and 109 triplets. The costs of infertility treatment were excluded as they were common to all study groups. The costing was conducted from a payer's perspective and costs were expressed in 2002 British Pounds. Results indicate that total direct costs per IVF pregnancy were £3313 for singletons, £9122 for twins, and £32,354 for triplets. IVF multiple pregnancies accounted for 1/3 of the total annual number of maternities but generated 56% of the total costs associated with IVF pregnancies. The authors concluded that IVF multiple pregnancies are associated with significantly higher costs than IVF singletons and thus, there is potential cost savings associated with SET policies. Limitations of the study were that it did not consider long term health and costs outcomes and that costs for antenatal care, outpatient visits, and postnatal home visits for twins and triplets were assumed to be the same for the singleton.

Cassell et al.[9] conducted a retrospective observational study comparing hospital costs between singleton, twin, and HOM pregnancies in Nova Scotia. Data was collected from a tertiary maternal hospital and the Nova Scotia Atlee Perinatal Database. Between January 1980 and December 2001 there were 113,222 singleton pregnancies, 1724 twin pregnancies, and 37 HOM pregnancies. Hospital costs were calculated based on maternal and neonatal length of stay.

The costing was conducted from a hospital payer's perspective expressed in 2002 Canadian dollars. Physician fees and the cost of extra radiological investigations were excluded from the study. Results indicate that the total hospital costs per pregnancy were $6750 for singletons, $39,430 for twins, $222,000 for triplets, and $278,400 for quadruplets. Higher costs associated with HOM pregnancies were due to longer length of stay and greater frequency of cesarean delivery, preterm labor, preeclampsia, and admissions to intensive care unit. Approximately 51% of the HOM pregnancies were a result of infertility treatment. The authors concluded that maternal morbidity, perinatal morbidity, mortality, and associated hospital costs are associated with HOM pregnancies. Limitations of the study were that it did not conduct a sensitivity analysis and it did not consider long term health and cost outcomes.

Koivurova et al.[10] conducted a retrospective observational study comparing health care costs between IVF and naturally conceived infants in Finland. Data on pregnancy, outpatient clinic visits, and hospital days were collected by a resident physician from hospital records. Cost data were collected from the National Research and Development Center for Welfare and Health and included cost of infertility treatment, physician consultation, and hospital care. The IVF study population consisted of 215 mothers (153 singletons and 62 twin pregnancies) and 255 infants (152 singletons and 103 twins). The non-IVF study population consisted of 662 mothers (580 singletons and 82 twin pregnancies) and 388 infants (285 singletons and 103 twins). The costing was conducted from a payer's perspective expressed in 2003 Euros. Results indicate that costs of an IVF singleton infant were higher than naturally conceived singleton (€5778.1 vs. €4495.6) while costs were comparable between IVF and naturally conceived twins (€15,579.5 vs. €14,447). The authors concluded that costs associated with IVF singletons are higher than naturally conceived singletons and multiple births increase health care costs. The authors suggest that reducing multiple pregnancies is the most effective means of reducing health care costs resulting from IVF. Limitations of the study were that it did not consider long term health and cost outcomes.

Lukassen et al.[11] conducted a retrospective observational study comparing health care costs between singleton and twin pregnancies after receiving IVF. Costs were compared from pregnancy until 6 weeks post delivery. Data was collected from the IVF population at the University Medical Center. The study population consisted of all couples with a live-born singleton or at least one live born twin after IVF treatment between 1995 and 2001. From this population, 172 most recent twin pregnancies and 168 singleton pregnancies with similar dates of embryo transfers were selected for the analysis. Costs include antenatal care, delivery, and maternal and neonatal admission days. Data on antenatal care, mode of delivery, days of maternal hospital admission, and days of neonatal hospital admission was obtained through mail out questionnaires. Unit costs were obtained from the Dutch National Health Tariffs Authority and were expressed in 2003 Euros. The costing was conducted from a payer's perspective. Results indicate that total costs were €10,920 higher per twin pregnancy than per singleton pregnancy (€2549 vs. €13,469). The authors concluded that medical costs from IVF pregnancies from pregnancy to 6 weeks post delivery per twin pregnancy were five times higher than per singleton pregnancy. Reducing the number of twin pregnancies by implementing single embryo transfer will save costs. The savings from SET could be used for additional IVF cycles needed to achieve similar success rates as double embryo transfer (DET). Strengths of the study were that it conducted a sensitivity analysis and a thorough costing analysis from a payer's perspective. Limitations of the study were that it did not include other relevant costs (e.g. ambulatory care and primary care utilization including physician visit costs) and it did not compare costs with a control group of non-IVF patients. Therefore, although the study showed IVF twins having higher costs than IVF singletons, the additional health care costs compared to non-IVF infants was unclear.

Ericson et al.[12] conducted a retrospective observational study comparing hospital utilization between IVF singleton, twin, and full term births in Sweden from birth to 14 years of age. Data was collected from 15 units where IVF was performed in Sweden. Between 1984 and 1997 there were 1,417,166 live births of which, 9056 were IVF births were identified. Singleton IVF infants had 3 more hospital days than non-IVF infants. When comparing IVF singletons and twins, twins were associated with 7.4 more hospital days (13 vs. 5.6). In 1996 there were approximately 1500 IVF infants born in Sweden. Before 6 years, excess hospital care would be estimated at 10,800 days, translating to 54×10^6 (at 5,000 SEK per hospital day) in excess hospital costs. Limitations with the study were that it did not include other relevant health service utilization outputs (e.g. ambulatory care and primary care utilization including physician visit costs). The study provides a direct link between ARTs related births and increased hospital utilization.

Costs and cost effectiveness of limiting embryo transfers

Little et al.[13] used a DAM to compare the health care costs between transferring one thru five embryos per IVF cycle for a hypothetical cohort of 10,000 women. Data inputs were based on existing published literature. The costing was conducted from three perspectives: insurer perspective (hospital costs and direct and indirect lifetime medical costs), patient's (cost of IVF treatment), and societal (payer and patient perspective). Costs were expressed in 2005 United States dollars. Results indicate that from a societal and insurer perspective, transferring one embryo is associated with the lowest total. From a patient perspective, transferring two embryos is associated with the lowest cost. However, transferring one embryo was associated with significantly improved health outcomes (e.g. preterm birth, LBW and cerebral palsy rate). The authors concluded that transferring one embryo per IVF cycle is the least expensive strategy from a societal perspective but the most costly from a patient's perspective. Strengths of the study were that it incorporated short and long term health and cost outcomes. Limitations of the study were that it did not indicate whether they used discounting to standardized costs to 2005.

Gerris et al.[14] conducted a prospective observational study comparing treatment, hospital, and outpatient costs between SET and DET (refer to Appendix B). Patients were recruited from two IVF/ICSI programs who were younger than 38 and who received treatment for infertility. There were 206 patients who received single embryo transfer and 161 who received double embryo transfer. The costing was conducted from both a payer's and a societal perspective. Costs included treatment, pregnancy, complicated pregnancy and neonatal costs up to 3 months post delivery. Unit costs were derived from published literature. Information regarding antenatal, obstetric, and neonatal services, including consultations, sonographies, blood examinations, medications, amniocentesis, and other examinations, were collected using case report forms given to patients at the time of their first sonograph. Costs reflected 2000-2001 costs expressed in Euros. Results indicate that the total cost was €7126 for a single embryo transfer with 37.4% (n=206) resulting in a live birth and €11,039 for a double embryo transfer with 36.6% (n=161) resulting in a live birth. The authors concluded that there is no difference in the ongoing clinical pregnancy rate or live delivery rate between women with good prognosis receiving single embryo transfer or double embryo transfer. The difference in cost between single and double embryo transfer is entirely attributed to the higher cost of twin pregnancies. Furthermore, because only one embryo is transferred per IVF cycle, a greater number of SET cycles will be needed to obtain the same pregnancy rate as DET. The authors speculate that there is no cost difference between SET and DET because the higher costs of double embryo transfer is offset by the greater number of single embryo transfer cycles needed to obtain the same number of children. The strength of the study is based on prospective design. The primary limitation of the study was that the number of live births was the primary outcome measure. The study did not formally include long term clinical and cost consequences associated with twin gestations and births which underestimate the cost associated with DET. Therefore, the net long term cost impact of SET compared with DET remains unresolved.

The Medical Advisory Secretariat[15] conducted a cost effectiveness analysis comparing IUI with SET IVF and DET IVF. Comparisons between alternatives were further divided by using all fresh embryos for SET and DET IVF or using frozen embryos for the second and third IVF cycles. The hypothetical study population consisted of women younger than 36 with non-tubal infertility and no previous IVF treatment history. Data for the model were derived from available literature and expert opinion. Costs included infertility treatment and physician and hospital costs for vaginal delivery, caesarean section, multiple births, and neonatal intensive care. The analysis was conducted from a payer's perspective and reflected in 2006 Canadian dollars. Results indicated that the cost per birth was $21,000 for IUI. When using fresh embryos for all three IVF cycles, the cost per birth was $33,000 for DET and $85,000 for SET. When using frozen embryos for the second and third IVF cycle, the cost per birth was $28,000 for DET and $50,000 for SET. The cost of providing SET in Ontario is approximately $9.8 to $12 million. The authors concluded that the costs of providing coverage for SET

IVF in Ontario are greater than the savings in short term hospital and physician costs associated with reducing multiple births. The major limitations of the study are that the authors calculated the ICER within IUI, SET, and DET and not between IUI, SET, and DET. Thus, the ICER reflects the cost per additional birth compared to no treatment (i.e. doing nothing) and not the cost effectiveness between the options. No sensitivity analysis was conducted on costs or model assumptions. The study did not incorporate long term health and costs outcomes which may underestimate the total cost associated with DET. Effectiveness was defined as successful live birth which ignores the health outcomes of the infants.

Fiddelers et al.[16] conducted a cost effectiveness analysis (CEA) alongside a randomized control trial (RCT) comparing the cost effectiveness of SET (n = 154 couples) to DET (n = 154 couples). The analysis was conducted from a societal perspective and included costs for both men and women. Costs included hospital, IVF procedure, prenatal/postnatal care, and general practitioner visits. Non-health care costs included lost productivity and out of pocket costs for couples (e.g. travel costs and over the counter medications associated with IVF treatment and resulting pregnancies). Costs were calculated for each couple from start of initial IVF treatment up to 42 weeks post embryo transfer. For pregnant patients, costs were calculated up to 4 weeks after delivery. Costs were expressed in 2003 British Pounds. Effectiveness was defined as a successful pregnancy (i.e. at least one live born child). Results indicate that total societal costs per couple were €7334 for elective single embryo transfer and €10,924 for double embryo transfer. Elective single embryo transfer had a positive ongoing (more than 12 weeks of pregnancy) pregnancy rate of 33.1% while double embryo transfer had a positive ongoing pregnancy rate of 40.3%. Of the successful pregnancies, 0% and 19.6% were twins after one cycle elective SET and DET, respectively. The incremental cost effectiveness ratio (ICER) of DET compared to elective SET was €19,096 per additional live birth. The authors concluded that in an unselective group of patients undergoing IVF treatment, one cycle elective SET is less expensive but also less effective compared with one cycle DET. Whether DET is cost effective depends on society's WTP for an extra successful live birth. The primary limitation of the study was that effectiveness was defined as successful live birth and the long term health outcomes of twin gestations and births were not included. It is important to note that twins are at increased risk for short and long term health outcomes compared to singletons.

Kjellberg et al.[17] conducted a CEA alongside a RCT comparing the cost effectiveness of one fresh IVF cycle SET and one frozen SET (if pregnancy did not occur with first cycle) with one fresh IVF cycle DET. The population consisted of 661 women (SET n = 330; DET n = 331) younger than 37 undergoing their first or second IVF cycle, but also having at least two quality embryos available. The analysis was conducted from both a payer's and societal perspective. Costs were collected from first IVF treatment to 6 months post delivery and included IVF treatment, required drugs, health complications, pregnancy, hospital costs, miscarriage, antenatal care, and general practitioner visits. Non-health care costs including lost productivity defined as the number of days absent from work which was primarily collected using questionnaires was included. Costs were expressed in 2004 Euros. Effectiveness was defined as a successful live birth. Results indicate that total costs for SET and DET was €3,069,989 and €4,077,155, respectively. The pregnancy rate was 38.8% for SET and 42.9% for DET. The ICER of DET compared to SET was €71,940 per additional live birth (€91,702 when including lost productivity costs). The authors concluded that the findings do not support DET. The primary limitation of the study was that effectiveness was defined as successful live birth and long term health outcomes associated with twin gestations and births were excluded.

De Sutter et al.[18] used a decision analytic model (DAM) to compare the cost effectiveness of single versus DET. The population consisted of 1000 hypothetical cohorts for both single and DET arms that reflected patients with good prognosis in light of available data being obtained in young patients with good embryo quality. Analysis was conducted from a payer's perspective despite the author's claiming it was societal (i.e. analysis only included direct medical costs). Costs included procedural cost of treatment, miscarriage, pregnancy, delivery (vaginal and caesarean), and neonatal stay. Costs were derived from the fertility program at the Gent University Hospital. Costs were made to reflect 2001 costs expressed in Euros. Effectiveness was defined as a successful live birth. Other model inputs (e.g. probabilities and rates) were obtained from available literature. Model and cost calculations commenced at time of embryo transfer and terminated with a live birth event. Results indicate that the ICER was €11,805 per child birth for SET compared to €10,966 per additional child birth for DET (cost results are not reported separately). The authors concluded that DET produces more children in fewer cycles but economically SET is equivalent to double embryo transfer. The authors also concluded that SET is more desirable than DET from a long term perspective due to a high risk of adverse health outcomes for twins compared to singletons, although the study did not include longer term consequences and costs in the model. There are three primary limitations of the study. Firstly, the authors calculated the ICER within SET and DET rather than between SET and DET. Thus, the ICER reflects the cost per additional birth compared to no treatment (i.e. do nothing). That is, compared to providing no treatment, SET costs €11,805 per birth while DET costs €10,966 per additional child birth. IHE was unable to calculate the ICER between SET and DET because costs were not reported separately from effectiveness outcomes. Secondly, the study does not incorporate long term health and cost outcomes which may underestimate the total cost associated with DET. Thirdly, effectiveness was defined as successful live birth which ignores the health status of the infants.

Cost impact of providing insurance coverage or regulator policies

Reynolds et al.[19] conducted a retrospective observational study determining whether insurance coverage for ARTs procedures were associated with fewer embryo transfers and decreased risk for multiple births in the United States in 1998 in women younger than 36 (insurance laws were in effect for 7 years). Three states with comprehensive infertility insurance laws (Illinois, Massachusetts, and Rhode Island) were compared with three states without comprehensive infertility insurance laws (Indiana, Michigan, and New Jersey). Four main outcomes were compared between insurance and non-insurance states: number of embryos transferred, proportion of multiple live births, proportion of triplet or HOM live births, and the proportion of triplet or HOM pregnancies. There were a total of 7561 IVF procedures, 3008 of which were conducted in non-insurance States. Results indicate that the three insurance states had protective odds ratios for triplets and HOM but only Massachusetts reached statistical significance. The authors concluded that insurance coverage does affect embryo transfer practices and patients younger than 36 undergoing IVF in states with mandated insurance coverage for ARTs were associated with fewer embryo transfers than those receiving IVF in states without mandated insurance coverage. Limitations of the study were that the analysis did not statistically control for potential confounders including systematic differences in patient populations, health systems and type of insurance coverage between States.

Jain et al.[20] conducted a retrospective observational study determining whether insurance coverage for ARTs procedures were associated with few embryo transfers and decreased risk for multiple births in the United States in 1998. Data on fertility clinics were separated by state and categorized into whether they provided complete, partial, or no coverage. Complete insurance coverage was defined as covering the cost of diagnosis and treatment including IVF. Partial coverage was defined as covering only partial cost of IVF or having a maximum lifetime benefit of $15,000. No coverage was defined as the absence of coverage for IVF. Of the 360 infertility clinics in the United States in 1998, 31 were in states requiring complete insurance coverage, 27 were in states requiring partial coverage, and 302 were in states that did not require coverage. Clinics in states that required complete coverage performed more IVF cycles (3.35 fresh embryo cycles and 0.43 frozen embryo transfers per 1000 women) compared to states requiring partial insurance (1.46 fresh embryo cycles and 0.30 frozen embryo transfers per 1000 women) and states with no insurance (1.21 fresh embryo cycles and 0.20 frozen embryo cycles per 1000 women). Compared to states with no coverage, the multiple birth rates were lower in states with partial (38.2% vs. 35.4%) or complete coverage (38.2% vs. 36%). The authors concluded that complete insurance coverage (compared to no coverage) was associated with a 277% increase in utilization of IVF services but were also associated with a reduction in the number of embryos transferred per IVF cycle. States that do not require insurance coverage have the highest number of embryos transferred per IVF cycle resulting in the highest rates of pregnancy and multiple births. Limitations of the study were that the analysis did not control for potential confounders including systematic differences in patient populations and health systems between states.

De Neubourg et al.[21] conducted a retrospective observational study determining whether legislated policies limiting the number of embryo transfers per IVF cycle affect multiple pregnancy rates in Belgium. On July 1, 2003, Belgium implemented legislation specifying the number of embryos that could be transferred in IVF including publicly funding IVF/ICSI laboratory costs. The Belgian IVF policy is as follows:

- For women younger than 36, one embryo transfer is allowed during the first and second cycle and two embryo transfers is allowed during the third to sixth cycle.
- For women between 36 and 39, two embryos transfers are allowed during the first and second cycle and three embryo transfers are allowed during the third to sixth cycle.
- For women between 40 and 42 there is no limit on the number of embryo transfers allowed for any cycle.

Pregnancy and birth rate data were collected from the centre for Reproductive Medicine at Middleheim Hospital between July 1, 2003 and June 20, 2004. Results indicate that the twin pregnancy rate was 8.5% compared to 24.4% prior to legislation. The authors concluded that introduction of legislation restricting the number of embryo transfers coupled with IVF/ICSI reimbursement has reduced multiple pregnancies in Belgium. Limitations of the study were that the analysis had a relatively short time horizon and that it could not differentiate the extent to which legislation or reimbursement accounted for the reduction in the multiple pregnancy rate.

Van Landuyt[22] conducted a retrospective observational study determining whether newly legislated policies limiting the number of embryo transfer per IVF cycle affect multiple pregnancy rates in Belgium (same legislation outlined in De Neubourg et al.[21]). Multiple pregnancy rates were compared between March 2002-June 2003 and July 2003-September 2004 by age (< 36 years, 36-39 years, and 40-42 years). Results indicate that the average number of embryos transferred decreased from 2.1 before legislation to 1.5 after legislation. The proportion of multiple pregnancies decreased from 29.1% before legislation to 9.5% after legislation with a reduction in twin gestations from 25.8% to 9.0% and a reduction in triplet gestations from 3.3% to 0.4%. However, the proportion of SET increased from 16.6% to 60.0% while the overall pregnancy rate decreased from 10.7% to 27.4%. The authors concluded that IVF legislation decreased multiple pregnancies but triplet pregnancies were not completely avoided. The slight decrease in clinical pregnancy is acceptable. Limitations of the study were that the analysis had a relatively short time horizon and that it could not differentiate the extent to which legislation or reimbursement accounted for the reduction in the multiple pregnancy rate.

Tiitinen et al.[23] conducted a retrospective observational study determining whether a policy of elective SET affected multiple birth rates at the Infertility Clinic of Helsinki University Central Hospital. In 1997, an elective SET policy was introduced and by 2001 was the only form of IVF being conducted, with the exception of DET being conducted in special cases. Between 1997 and 2001, there were 1871 IVF cycles with 1699 total embryo transfers. Of the total embryo transfers, 1024 were elective SET, 470 were DET, and 205 were in cases where only one embryo was available. The mean age of the women were 33.4 years of age with a range of 20.5 to 41.9 years of age. Data was analyzed to compare the clinical pregnancy rate, delivery rate per embryo transfer and the multiple birth rate. Results indicate that the number of embryos transferred per IVF cycle decreased from 1.8 to 1.3 but the clinical pregnancy rate remained stable with an average of 34%. The multiple pregnancy and delivery rates were reduced from 25% to 7.5% and from 25% to 5%, respectively. The authors concluded that SET clearly reduces the risk of twin pregnancy with acceptable pregnancy and delivery rates. Limitations of the study include the fact that data come from one fertility centre, and the majority of the women were younger than 37.

Summary

Seven studies provided economic evidence to inform whether ARTs are associated with increased health care costs. Overall, the evidence suggests multiple embryo transfer IVF contributes to higher health care costs because twins and HOM are at increased risk of maternal and fetal/birth complications (both short and long term). Limitations of the evidence were the exclusion of other relevant cost impacts such as physician visits, outpatient service utilization, and long term costs including, but not limited to, cerebral palsy, learning disabilities, and other associated chronic conditions.

Two studies provided evidence that when comparing both SET and DET to no IVF treatment, the cost per birth of SET was higher than DET. However, when comparing SET directly to DET, four studies provided evidence that DET is associated with greater health services costs due to health complications associated with twin pregnancies and births (short term horizon). However, the effectiveness of SET to produce a live birth depends on women's age. In women younger than 37, transferring one embryo is as effective as transferring two embryos but is less effective in women older than 37. Therefore, in women older than 37, more SET IVF cycles will be required to achieve comparable birth rates as DET IVF. However, it is important to recognize that the studies comparing the cost effectiveness of SET to DET did not incorporate long term health and cost outcomes and define effectiveness as a successful live birth (ignores health of infant). As a result, these studies underestimate the costs of DET and the effectiveness of SET at producing a healthy baby given that twins are at greater risk for short and long term health complications.

Five studies evaluated the impact of IVF reimbursement and policies of SET on health care resources. Overall, an association was observed between IVF reimbursement and a decrease in multiple birth rates. IVF reimbursement was also associated with increased utilization of IVF services and the number of SET cycles.

Conclusion

In conclusion, the evidence suggests that reducing the number of embryos transferred per IVF cycle is associated with decreasing health services costs. SET is potentially cost effective compared to DET, particularly when incorporating long term health outcomes and defining effectiveness as generating a healthy live birth. Reimbursing SET IVF is associated with decreasing multiple birth rates but also increased utilization of IVF services. Note that there were no studies that evaluated the costs and effectiveness of PGD.

Section 2: Preliminary Analyses of Available Alberta Health and Wellness Data

While there is evidence that ARTs are associated with increased health services costs and that policies aimed at reducing the number of embryos transferred per IVF cycle could potentially reduce costs, estimating the magnitude of potential cost savings first requires an assessment of the cost burden associated with multiple pregnancies/births in the Alberta context. The objective of this section is to explore the impact of multiple births and LBW infants on health resource utilization and costs in Alberta.

Population

The population cohort was comprised of mothers and infants born between April 1, 2004 and March 31, 2005. Mothers and infants were identified by reviewing the Hospital Inpatient database for birth events, which include health records for both infants and mothers. Health services cost data for infants represented 1 year cost from birth and therefore comprised data collected from April 1, 2004 to March 31, 2006. Health services cost data for mothers represented 1 year costs from pregnancy until 3 months post partum and therefore comprise data collected from July 1, 2003 to June 30, 2005. Identified infants were categorized as LBW and NBW infants. Low birth weight was defined as weighing < 2500 grams and normal birth weight weighing > = 2500 grams. Infants were further categorized as a singleton, twin, or HOM.

Cost Data

Cost data was received from AHW on February 22, 2008. Cost data was extracted from two Alberta provincial health ministry databases. The Hospital Inpatient database provided information related to hospital utilization costs. Each hospital admission is assigned a case mix group (CMG) according to the classification system developed by the Canadian Institute for Health Information (CIHI)[24] and a corresponding resource intensity weight (RIW), which is an index of resource use that corresponds to the case mix group. The cost per weighted case (provided by CIHI) is multiplied by the RIW providing a cost for each procedure/intervention. Inpatient cost data were provided separately for mothers and infants. Information contained in the inpatient datasets included an anonymized patient code, length of stay, infant weight group, and the "best available cost" associated with each hospital event for each infant (over 1 year after birth) and mother (from pregnancy to 3 months post partum). Best available cost refers to using the actual cost listed with the hospital procedure but if absent, an average cost (2004/2005 average) associated with the procedure/intervention was used instead.

The Alberta Health Care Insurance Plan database provided information related to billing services and ministry payments to physicians for medically insured services in Alberta. Physician cost data were provided separately for mothers and infants. Information contained in the dataset received from AHW for both mothers and infants included an anonymized patient code, physician specialty, and amounts paid. Cost data on ambulatory care service utilization were unavailable at the time of the analyses.

Statistical analyses

Table 2-A summarizes the analyses that were conducted with the data provided. First, logistic regression was used to determine whether twins and HOM had greater likelihood of being born LBW than singletons in Alberta. The evidence indicates that ARTs generate a disproportional number of twins/HOM which are more likely to be born LBW. It was therefore important to measure the association between plurality and birth weight in the data.

Second, a series of linear regressions was used to estimate the impact of multiple births and low birth weight infants on health service resource utilization and costs. Analyses were conducted separately for infants and their mothers on both costs and number of visits.[1] The general form of the linear regression model is shown below (refer to Appendix D for the specific model specification of each regression model).

$$Y = \beta_0 + \beta_1 \times Plurality + \beta_2 \times Birthweight + \beta_3 \times (Plurality \times Birthweight)$$

This general form of the linear regression model not only determines whether costs/visits are statistically different between plurality (i.e. between singletons, twins, and HOMs) and between birth weight (i.e. between NBW and LBW infants), but it also determines whether an interaction exists between plurality and birth weight. This interaction further categorizes plurality by birth weight and identifies whether there is a difference in costs or visits that is not anticipated on the basis of plurality or birth weight independently. Statistical significance was defined as $p < 0.05$. All analyses were conducted with STATA 9.1 (Statacorp LP, College Station, Texas).

1 Regression models for costs did not include the number of visits due to issues of endogeneity and lack of available instrumental variables.[25] Endogeneity refers to a situation where the independent (e.g. visits) and dependent variables (e.g. costs) are co-dependent resulting in biased regression coefficients. An instrumental variable is a variable that can substitute for the endogenous independent variable.

Table 2-A: Summary of statistical analyses

Questions	Analysis	Rationale
Are twins and HOM more likely to be of LBW than singletons?	Logistic Regression	Determine the probability of being born LBW based on plurality
INFANTS		
Are total costs different between LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in total costs are statistically significant
Are hospital costs different between LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in hospital costs are statistically significant
Are physician costs different between LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in physician costs are statistically significant
Are total hospital visits different between LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in hospital visits are statistically significant
Are total physician visits different between LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in physician visits are statistically significant
MOTHERS		
Are total costs different between mothers of LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in total costs are statistically significant
Are hospital costs different between mothers of LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in hospital costs are statistically significant
Are physician costs different between mothers of LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in physician costs are statistically significant
Are total hospital visits different between mothers of LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in hospital visits are statistically significant
Are total physician visits different between mothers of LBW and NBW singletons, twins, and HOM infants?	Linear Regression	Determine whether difference in physician visits are statistically significant

Exclusion criteria for costs and visits

A small proportion of pregnancies often account for a large proportion of health services costs resulting in a skewed distribution of costs.[11] It was not possible to identify individual specific costs and visits that were directly attributable to pregnancy and birth plurality in the data provided. Nonetheless, to increase the validity of comparisons between study groups, it was imperative that the data analyses exclude extraneous costs and visits that likely do not reflect the average costs/visits associated with birth plurality.

In the absence of being able to attribute individual costs and visits to pregnancy and birth plurality, the distribution and skew of the data was explored to determine the appropriate inclusion criteria for including costs and visits (see Appendix C). Final inclusion criteria were based on achieving parsimony between minimizing skew while maximizing sample size. This necessitated that skew be assessed separately for visits and costs for each data set as the distribution of costs and visits vary between physician costs, hospital costs, physician visits, and hospital visits for infants and mothers.

It was determined that infant hospital costs, infant physician costs, infant physician visits, and mother hospital costs were positively skewed (i.e. high cost/visit outliers) and parsimony was achieved using a criterion of three times the standard deviation (i.e. costs and visits exceeding three times the standard deviation were censored from the data analyses).

In addition, it is important to note that there were 134 mothers who gave birth to twins or HOM who were a combination of LBW and NBW infants. There was no means of separating costs by birth weight for mothers of infants with mixed birth weights based on information from the database and these mothers were censored from further analysis.

Sensitivity Analysis

Although it is important to minimize skew when making mean comparisons in costs between comparison groups, eliminating outliers does introduce the potential of underestimating costs[11] and visits because it may exclude costs/visits that are related to pregnancy and birth plurality. Therefore, in a sensitivity analysis we analyzed all cost and visit data without excluded outliers.

Results

All costs represent 2006 Canadian Dollars.

Descriptive

There were 36,158 mothers and 36,767 infants in the data sets (see Table 2-B). Of the 36,767 infants, 35,495 were singleton (96.5%), 1227 were twins (3.3%), and 45 (0.12%) were HOM. The proportion of NBW infants for singletons, twins, and HOM were 95%, 52%, and 4%, respectively.

It is noteworthy to mention that there were 134 mothers who gave birth to twins or HOM who were a combination of LBW and NBW with no means of separating costs by birth weight for mothers of infants with mixed birth weights based on information from the database. Consequently, the 134 cases were censored from further cost analyses. Dropping the cases did not affect the analysis because they represent only 0.37% of the total cases included in the analysis of mother costs and visits.

Table 2-B: Summary of population

Birth weight	Singletons		Twins		HOM		Total	
	Number	%	Number	%	Number	%	Number	%
INFANTS								
NBW	33,824	95.29%	633	51.59%	2	4.44%	34,459	93.72%
LBW	1671	4.71%	594	48.41%	43	95.56%	2308	6.28%
Total	35,495	100%	1227	100%	45	100%	36,767	100%
MOTHERS								
NBW	33,978	95.30%	255	41%	0	0.00%	34,233	94.33%
LBW	1677	4.70%	234	37.62%	14	93.33%	1925	5.30%
Mixed	0	0%	133	21.38%	1	6.67%	134	0.37%
Total	35,655	100%	622	100%	15	100%	36,292	100%

Note: Table presents summary statistics for entire sample population. LBW=Low birth weight; NBW=Normal birth weight; Mixed=Mixed birth weight (i.e. twins or HOM were a combination of LBW and NBW infants)

Table 2-C shows the average costs and visits for infants and mothers. For infant data, compared to singletons, twins and HOM were associated with $5543 and $15,815 higher hospital costs and $8332 and $1275 higher physician costs, respectively. Compared to singletons, twins and HOM were associated with 0.2 and 1.1 greater hospital visits and 2.5 and 11.9 greater physician visits. For mothers data, compared to mothers who gave birth to singleton infants, mothers who gave birth to twins and HOM were associated with $1615 and $2943 higher hospital costs and $411 and $647 higher physician costs, respectively. Compared to singletons, twins and HOM were associated with 0.24 and 0.7 greater hospital visits and 11.7 and 21.7 greater physician visits.

Table 2-C: Summary of costs and visits

Group	Variable	Infants			Mothers		
		N	Mean	Standard Deviation	N	Mean	Standard Deviation
Singleton	Hospital Costs	35,125	$2265	$4529	34,841	$2773	1343
	Physician Costs	35,076	$580	$427	35,655[a]	$2088[a]	1024[a]
	Hospital Visits	35,495[a]	1.19[a]	0.61[a]	35,655[a]	1.18[a]	0.54[a]
	Physician Visits	34,820	12.10	6.74	35,655[a]	28.07[a]	12.42[a]
Twin	Hospital Costs	1144	$7808	$9982	416	$4388	1695
	Physician Costs	1157	$8912	$650	489[a]	$3320[a]	1410[a]
	Hospital Visits	1227[a]	1.41[a]	0.91[a]	489[a]	1.44[a]	0.81[a]
	Physician Visits	1130	14.60	8.24	489[a]	39.69[a]	17.92[a]
HOM	Hospital Costs	23	$18,080	$12,994	4	$5716	1948
	Physician Costs	39	$1855	$901	14[a]	$3952[a]	1671[a]
	Hospital Visits	45[a]	2.24[a]	1.58[a]	14[a]	1.93[a]	1.14[a]
	Physician Visits	38	24.00	7.75	14[a]	49.71[a]	21.64[a]

a. No cases were excluded for infant hospital visits, mother physician costs, mother hospital visits or mother physician visits. Skew was assessed separately for visits and costs for each data set. Refer to Appendix C for further details.

Regression analyses

Logistic regression

Table 2-D shows the results from the logistic regression. The logistic regression analysis was conducted on all 36,767 infants in the dataset. Compared to singletons, twins and HOM were 43.8% and 90% more likely to be born LBW, respectively. Compared to twins, HOM were 46.2% more likely to be born LBW.

Table 2-D: Probability of LBW by plurality

Variables	β	Standard Error	p value	Predicted Probability
Constant (singletons)	-3.008	0.025	<.001	4.7%
Twins	2.941	0.062	<.001	48.5%
HOM	6.076	0.724	<.001	94.7%
N = 36,767 Nagelkerke R Square = 0.145				

Linear regression

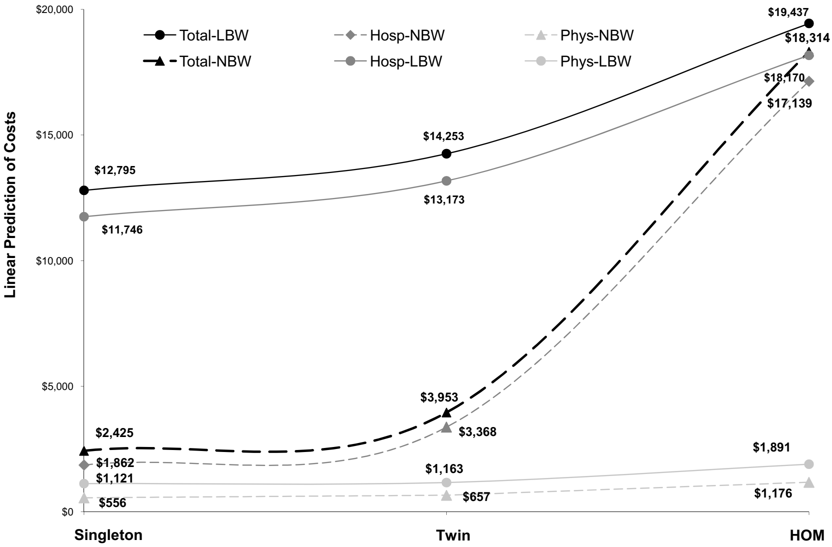
Note that an analysis of the residuals from all linear regression models indicates that statistical assumptions were satisfied.

Costs

Figure 2-A shows the predicted mean hospital and physician costs of infants (refer to Appendix E to contrast with results when not excluding outliers). There were statistically significant differences ($p < .05$) in physician, hospital, and total costs observed between NBW and LBW infants and between singletons, twins, and HOM (refer to Appendix D for full regression coefficients). Furthermore, there was a statistically significant interaction effect observed between LBW/NBW singletons and LBW/NBW HOM for hospital and total costs. There was also a statistically significant interaction effect observed between LBW/NBW singletons and LBW/NBW twins for physician costs.

NBW singletons were associated with the lowest mean total cost ($2425), followed by NBW twins ($3953), LBW singletons ($12,795), LBW twins ($14,253), NBW HOM ($18,314), and LBW HOM ($19,437) (see Table 2-E). Compared to NBW singletons, total costs were 1.63 times greater for NBW twins ($1528 more), 5.28 times greater for LBW singletons ($10,370 more), 5.88 times greater for LBW twins ($11,828 more), 7.55 times greater for NBW HOM ($15,889 more), and 8.01 times greater for LBW HOM ($17,011 more).

Figure 2-A: Hospital and physician costs for infants



Note: Skew was assessed separately for hospital costs, physician costs and total costs. Refer to Appendix B for further details.

Hosp: N=36,292 R-squared = 0.2294   Phys: N=36,272 R-squared =0.0993   Total: N=36,278 R-squared = 0.2245

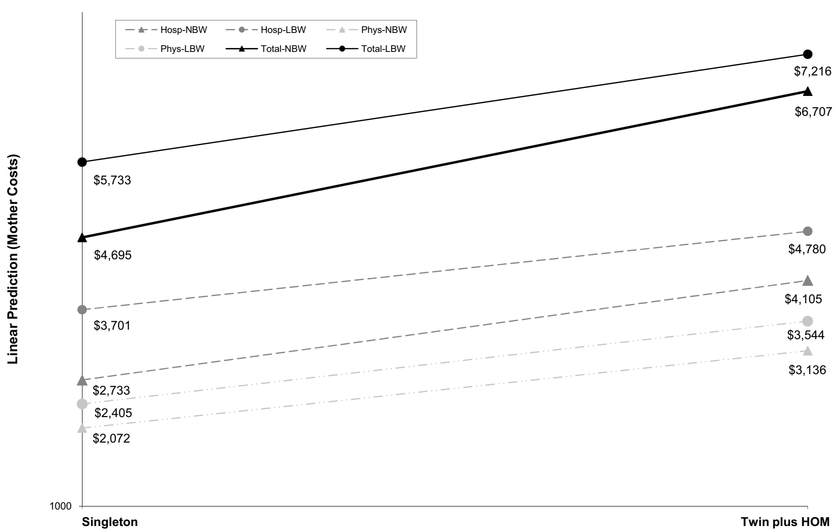
Table 2-E: Comparison of infant total costs

Birth Weight	Plurality	Linear Prediction of Mean Total Cost	Cost Difference Compared to NBW Singletons	Cost Ratio (Compared to Singletons)
NBW	Singleton	$2425	—	—
NBW	Twin	$3953	$1528	1.63
LBW	Singleton	$12,795	$10,370	5.28
LBW	Twin	$14,253	$11,828	5.88
NBW	HOM	$18,314	$15,889	7.55
LBW	HOM	$19,437	$17,011	8.01

Figure 2-B shows the predicted hospital and physician costs of mothers (refer to Appendix E to contrast with results when not excluding outliers). There were no HOM infants who were of LBW in the data set for mothers' costs and therefore the interaction between birth weight and HOMs could not be entered separately in the regression model. Thus, twins and HOM were grouped together and the figure presents the predicted mean costs for singletons and ≥ twins (i.e. twins or HOM). There were statistically significant differences ($p < .05$) in physician, hospital, and total costs observed between NBW and LBW infants and between singletons and ≥ twins (refer to Appendix D for full regression coefficients). Furthermore, there was a statistically significant interaction effect observed between LBW/NBW singletons and LBW/NBW ≥ twins for hospital and total costs.

Mothers of NBW singletons were associated with the lowest mean total cost ($4695), followed by mothers of LBW singletons ($5733), mothers of NBW ≥ twins ($6707), and mothers of LBW ≥ twins ($7216) (see Table 2-F). Compared to mothers of NBW singletons, total costs were 1.22 times greater for mothers of LBW singletons ($1039 more), 1.43 times greater for mothers of NBW ≥ twins ($2012 greater) and 1.54 times greater for mothers of LBW ≥ twins ($2521 greater).

Figure 2-B: Hospital and physician costs for mothers



Note: Skew was assessed separately for hospital costs, physician costs and total costs. Refer to Appendix B for further details. There were no HOM infants who were of LBW in the data set for mother's costs and therefore HOM could not be entered separately in the regression model. Therefore the figure presents the linear prediction of costs of singletons and ≥twins.

Hosp: N=35,261 R-squared =0.0371; Phys: N=36,158 R-squared = 0.0249; Total: N=34,787 R-squared = 0.0276

Table 2-F: Comparison of mothers total costs

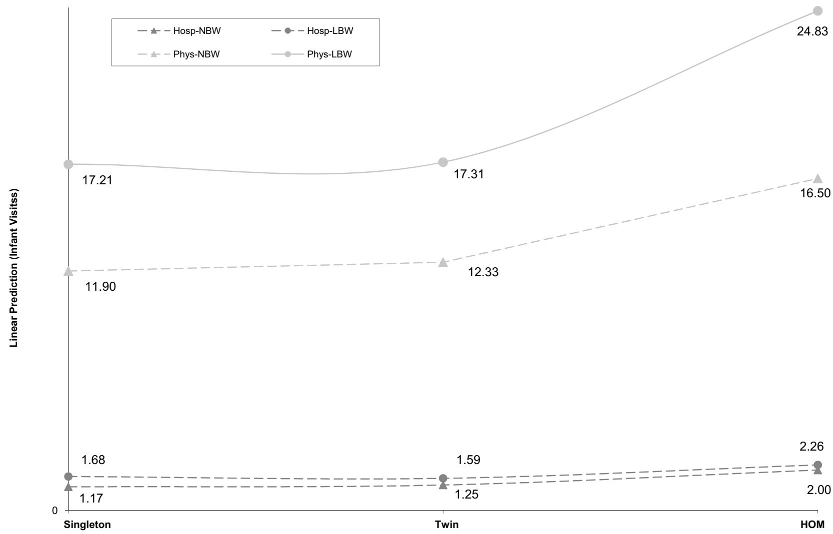
Birth Weight	Plurality	Linear Prediction of Mean Total Cost	Cost Difference Compared to NBW Singletons	Cost Ratio (Compared to Singletons)
NBW	Singletons	$4695	—	—
LBW	Singletons	$5733	$1039	1.22
NBW	≥ Twins	$6707	$2012	1.43
LBW	≥ Twins	$7216	$2521	1.54

Visits

Figure 2-C shows the predicted mean physician and hospital visits of infants (refer to Appendix D for full regression coefficients). For hospital visits, there were statistically significant differences ($p < .05$) observed between NBW and LBW infants and between singletons and twins. There was also a statistically significant interaction effect observed between LBW/NBW singletons and twins. For physician visits, there were statistically significant differences ($p < .05$) observed between NBW and LBW infants but no statistical difference between singletons, twins, and HOM. NBW singletons were associated with the lowest mean hospital visits (1.17) followed by NBW twins (1.25), LBW twins (1.59), LBW singletons (1.68), NBW HOM (2.00), and LBW HOM (2.26). NBW singletons were associated with the lowest mean physician visits (11.90) followed by NBW twins (12.33), NBW HOM (16.50), LBW singletons (17.21), LBW twins (17.31), and LBW HOM (24.83).

Figure 2-D shows the predicted mean physician and hospital visits of mothers (refer to Appendix D for full regression coefficients). There were statistically significant differences ($p < .05$) in physician and hospital visits observed between NBW and LBW infants and between singletons and ≥ twins. There was no interaction effect observed between LBW/NBW singletons and ≥ twins. Mothers of NBW singletons were associated with the lowest mean hospital visits (1.17) followed by mothers of NBW ≥ twins (1.33), mothers of LBW singletons (1.46), and mothers of LBW ≥ twins (1.58). Mothers of NBW singletons were associated with the lowest mean physician visits (27.90) followed by mothers of NBW ≥ twins (37.24), mothers of LBW singletons (31.56), and mothers of LBW ≥ twins (42.77).

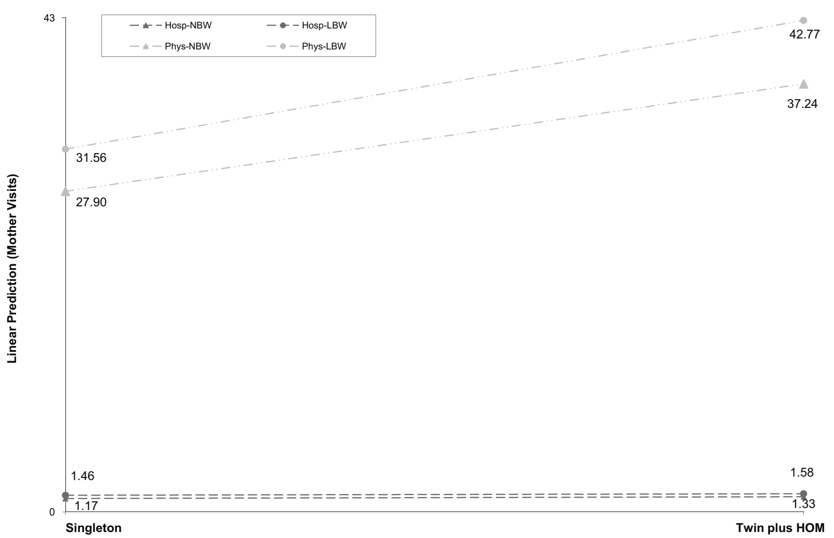
Figure 2-C: Linear prediction of infants visits



Note: Skew was assessed separately for hospital visits and physician visits. Refer to Appendix B for further details.

Hosp: N=36,767 R-squared =0.0387; Phys: N=35,988 R-squared =0.0347

Figure 2-D: Linear prediction of mothers visits



Note: Skew was assessed separately for hospital visits and physician visits. Refer to Appendix B for further details. There were no HOM infants who were of LBW in the data set for mothers' costs and therefore HOM could not be entered separately in the regression model. Therefore, the figure presents the linear prediction of costs of singletons and ≥ twins.

Hosp: N=36,158 R-squared =0.0161; Phys: N=36,158 R-squared =0.0167

Discussion

Comparisons between plurality and birth weight

Greater health services costs were observed in LBW infants (compared to NBW infants), twins (compared to singletons), and HOM (compared to singletons). This is not surprising because costs are expected to increase with greater birth plurality and lower birth weight. However, an interaction effect was observed between increasing plurality and lower birth weight indicating that LBW twins and LBW HOM are associated with significantly higher hospital and physician costs than singletons. In fact, the mean total cost of LBW twins and LBW HOM were respectively, 5.88 ($14,253 vs. $2425) and eight times ($19,435 vs. $2425) greater than that of NBW singletons.

The significantly greater health services costs associated with twins and HOM is particularly relevant in relation to ARTs because twins and HOM were found to be highly predictive of being born LBW in the data and ARTs are associated with generating disproportionately greater birth pluralities. Twins had a 49% probability of being LBW and HOM had a 95% probability of being LBW (singletons had a 4.6% chance of being born LBW).

Furthermore, the greater health care costs associated with twins and HOM (compared to singletons) were not likely driven by the volume of total visits. Although there were statistically significant differences in the number of hospital visits observed between singletons, twins, and HOM, the differences were small in magnitude (less than one visit) and no statistically significant differences were observed for physician visits. This suggests that the greater costs associated with twins and HOM (compared to singletons) are attributed to experiencing more severe health conditions.

Results for mothers were similar to infants. While health services costs were greater for mothers of twins and HOM (compared to singletons) and for mothers of LBW infants (compared to NBW infants), the combination of greater plurality and lower birth weight significantly increased health services costs. Furthermore, greater costs observed in mothers of twins and HOM (compared to mothers of singletons) are likely attributed to experiencing more severe health conditions.

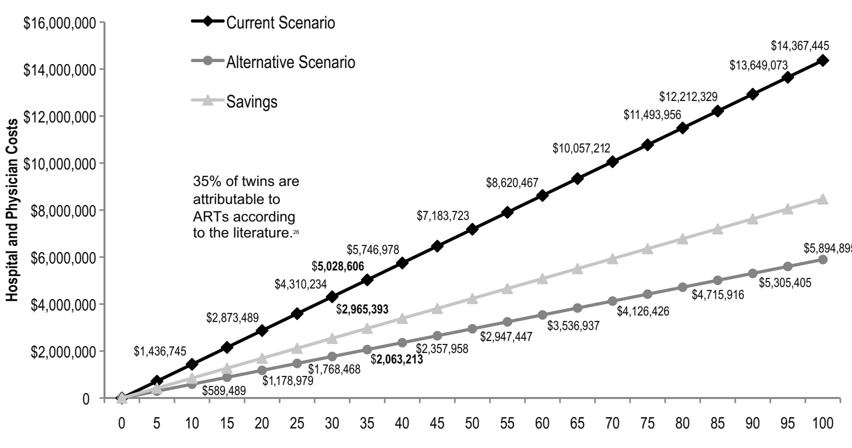
Costs potentially attributable to ARTs

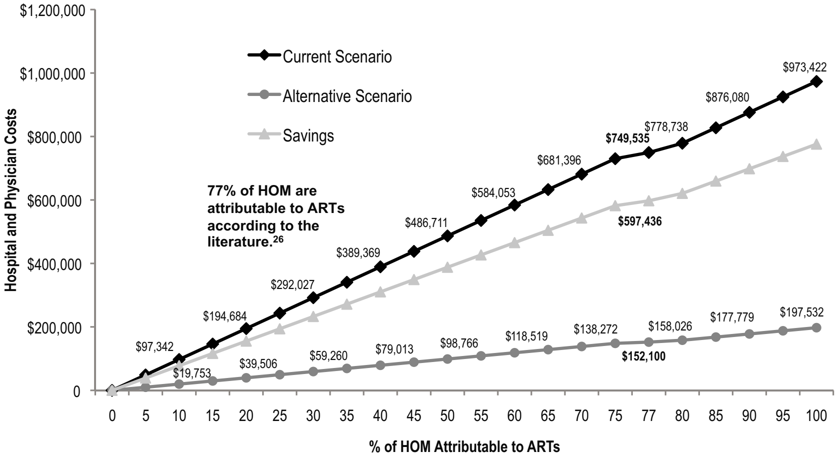
The available data did not identify which pregnancies resulted from ARTs procedures. Consequently, estimating the health services costs attributable to ARTs requires an assumption regarding the proportion of twins and HOM births attributable to ARTs procedures. Furthermore, estimating the potential cost savings had these twins and HOM been singleton pregnancies needs to account for the proportion of singletons that would still have been born LBW.

Figure 2-E shows the total costs and potential savings (refer to Appendix F for details of the cost calculations) for a range of possible proportions of infants attributable to ARTs procedures adjusted for birth weight. The current scenario represents the total health services costs of twins and HOM from the data while the Alternative Scenario represents the total health service costs had twins and HOM been instead singletons.

The total cost (hospital + physician of both mothers and infants) of twins and HOM to the Alberta health system is estimated to be $14,367,445 and $973,422, respectively ($15,340,867 in total). Assuming that 35% and 77% of Alberta twins and HOM can be attributed to ARTs,[26] the total cost of ARTs twins and HOM is $5,028,606 and $749,535, respectively, for the Current Scenario, and $2,063,213 and $152,100, respectively, for the Alternative Scenario. Therefore, the total estimated cost saving to the Alberta health care system had ARTs twins and HOM been instead singletons, is $2,965,393 and $597,436 respectively ($3,562,829 in total).

Figure 2-E: Potential cost savings had twin/HOM been singletons





Summary and Conclusion

Based on the cost analyses of AHW physician and hospital cost data for mothers and their infants born between April 1, 2004 and March 31, 2005, three main points emerge:

1. In Alberta, the probability that a twin and HOM will be LBW is 49% and 95%, respectively (44% and 90% more likely than singletons). In light of health services costs being significantly greater in LBW twins and LBW HOM compared to singletons as a result of greater morbidity (as opposed to greater frequency of service utilization), ARTs twins and HOM generate unnecessary morbidity and associated health services costs.

2. The estimated total health services costs of twins and HOM in Alberta is $15,340,867. Assuming that 35% and 77% of twins and HOM are a result of ARTs procedures, the estimated total health services costs attributable to ARTs twins and HOM is $5,778,141 (38% of total health services costs of twins and HOM). Note that long term health outcomes for infants have not been included in the current estimate.

3. Reducing the number of ARTs twins and HOM to singletons could have potentially saved $3,562,829 in hospital and physicians costs. However, if SET IVF is publicly funded, the potential savings associated with reducing the number of ARTs twins and HOM to singletons will be offset by the additional number of singleton cycles/procedures required to produce a singleton birth.

Caveats and Limitations of Current Evidence

When interpreting the evidence from Sections 1 and 2 of this report it is important to note main caveats:

1. The studies included in the review had short time horizons. The evidence regarding cost impacts of ARTs do not incorporate the downstream costs (e.g. cerebral palsy and learning disabilities) associated with twin and HOM pregnancies and births. Furthermore, the cost estimates from the studies included in the review primarily focused on hospital costs.
2. Effectiveness in the cost effectiveness studies was defined as a successful live birth, which ignores the short and long term health and cost complications associated with twins and HOM births (i.e. live birth does not equate a healthy infant). Operationalising effectiveness as a successful live birth bias the studies to favour DET.
3. This report does not examine whether the findings on IVF coverage and policies of SET (in Section 1) are generalisable to Alberta in terms of ethical and/or cultural differences in the countries where the studies took place (e.g. Belgium vs. Canada) nor does it examine how ethical and cultural considerations might impact the delivery and accessibility of ARTs services in Alberta.
4. The cost data analysed in Section 2 reflect short term direct health services costs, does not include ambulatory costs, and does not identify which pregnancies/births were a result of ARTs procedures. Therefore, there remains a great degree of uncertainty regarding the validity of the estimated overall cost impact of ARTs and the estimated magnitude of potential cost savings had twins and HOM births been singletons.
5. Based on the data provided by AHW, it was not possible to identify specific costs and visits that were directly attributable to pregnancy and birth plurality. Hence, outliers were excluded to derive an estimate of the average cost/visit associated with pregnancy and birth plurality. This method however, introduces the potential of excluding costs that are related to a pregnancy and birth plurality, which results in underestimating the average costs and visits. The sensitivity analysis did indicate that mean costs were significantly reduced after excluding outliers.
6. Data provided by AHW did not allow the statistical analysis to control or explore other potential relevant cost and background factors (e.g. mother's age or socioeconomic status). This is evidenced by the low R-squared values (refer to Appendix D) in the regression models which indicates that the variance in costs were not sufficiently explained by birth weight and plurality alone.

7. The evidence does not inform how ARTs will impact the health care system with changes in the prevalence of infertility. For policy making and planning, it would be insightful to estimate the cost impact of ARTs with fluctuations in the infertility rate and resulting changes in the demand for ARTs services.

Conclusion

Multiple embryo transfer IVF is the single greatest contributor to prematurity and long term health complications because of the resulting twins and HOM births.[27] The evidence indicates that the most effective approach for reducing costs associated with ARTs is to reduce the number of embryo transfers per IVF cycle. In Alberta, SET could have potentially saved $5,778,141 to the Alberta health care system. However, compared to multiple embryo transfer IVF, greater numbers of SET cycles are required to produce adequate birth rates. Thus, if specific components of ARTS such as SET IVF are to be publicly funded, cost savings will be offset by the increased number of SET cycles required to maintain acceptable singleton birth rates.

Comparing the cost of conducting additional SET cycles to the cost savings from reducing multiple births can be provided with further analysis. Such an analysis can also incorporate other relevant factors including the infertility rate, public demand for ARTs services, costs of ARTs services and the health services costs for short and long term health outcomes.

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Appendix A: Search Strategy

General Information

The literature search was conducted by the IHE Research Librarian for publications published between 2002 and 2007.

Medical Subject Headings (MeSH) terms relevant to this topic are:

† *See below for limits*

Database	Edition or date searched	Search Terms ††
The Cochrane Database of Systematic Reviews http://www.thecochranelibrary.com	Jan 8, 2008	#1 MeSH descriptor Reproductive Techniques, Assisted explode all trees #2 MeSH descriptor Pregnancy, Multiple explode all trees #3 MeSH descriptor Multiple Birth Offspring, this term only #4 (#1 OR #2 OR #3) #5 MeSH descriptor Costs and Cost Analysis explode all trees #6 (economic* OR cost*):ti,kw #7 (#6 OR #5) #8 (#4 AND #7) (0 results in CDSR)
MEDLINE OVID Licensed Resource	Jan 8 ,2008	1. reproductive techniques/ 2. exp Reproductive Techniques, Assisted/ 3. exp Pregnancy, Multiple/ 4. Multiple Birth Offspring/ 5. 1 or 2 or 3 or 4 6. exp “Costs and Cost Analysis”/ 7. (cost$ or economic$ or expenditures or price or fiscal or financial).ti. 8. 6 or 7 9. 5 and 8 10. limit 9 to animals 11. 9 not 10 12. limit 11 to (comment or editorial or letter or news or newspaper article) 13. 11 not 12 14. limit 13 to yr=”2002 - 2008” (143 results)

Database	Edition or date searched	Search Terms ††
Pubmed (www.pubmed.org)	Jan 8, 2008	1. embryo transfer OR assisted reproductive technolog* OR "assisted reproductive techniques" OR assisted conception OR in vitro fertilization OR IVF OR gonadotrophin stimulation 2. multiple birth* OR multiple gestation* OR (multiple AND pregnanc*) 3. cost or costs or costing or economic or economics or expenditures[title] or price[title] or fiscal[title] or funding[title] or financial[title] 4. (#1 OR #2) AND #3 5. pubmednotmedline[sb] or publisher[sb] or in process[sb] 6. #4 AND #5 Limits: Publication Date from 2002 (31 Results)
CRD Databases (DARE, HTA & NHS EED) http://nhscrd.york.ac.uk	Jan 8, 2008	# 1 MeSH Reproductive Techniques, Assisted EXPLODE 1 # 2 MeSH Pregnancy, Multiple EXPLODE 1 # 3 MeSH Multiple Birth Offspring # 4 #1 OR #2 OR #3 RESTRICT MD 2002 2008 (NHS EED Results = 75) Rest of search only on DARE and HTA database #5 cost* OR economic* #6 #4 AND #5 (HTA 6 results) (DARE 10 results)
EMBASE Licensed Resouce (Ovid Platform)	Jan 8, 2008	1. exp infertility therapy/ 2. (Assisted reproductive techniques or assisted reproductive technolog*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] 3. exp Multiple Pregnancy/ 4. 1 or 2 or 3 5. "cost"/ or exp "health care cost"/ 6. (cost$ or economic$ or expenditures or price or fiscal or financial).ti. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2002 - 2008" 10. limit 9 to (editorial or letter or note) 11. 9 not 10 (366 results)

Database	Edition or date searched	Search Terms ††
Web of Science ISI Interface Licensed Resource		1. embryo transfer OR assisted reproductive technolog* OR "assisted reproductive techniques" OR assisted conception OR in vitro fertilization OR IVF OR gonadotrophin stimulation OR gonadotropin stimulation 2. multiple birth* OR multiple gestation* OR (multiple AND pregnanc*) 3. cost or costs or costing or economic or economics or expenditures[title] or price[title] or fiscal[title] or funding[title] or financial[title]
Scopus? Licensed Resource		
NEOS Library http://www.library.ualberta.ca/catalogue	Jan 8, 2008	**Any field** "cost$ or economic$" **AND** **Any field** "in vitro fertilization OR assisted reproductive tech$ OR IVF OR infertility OR insemination OR multiple birth$ OR multiple pregnanc$" (2 relevant results)
Clinical Practice Guidelines (Background)		
AMA Clinical Practice Guidelines http://www.topalbertadoctors. org/TOP/CPG/CPGTopics.htm	Jan 9, 2008	Browsed for relevant guidelines (0 results)
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	Jan 9, 2008	IVF; assisted reproductive; insemination; fertilization; multiple birth*; multiple gestation* (two relevant results)
National Guideline Clearinghouse http://www.ngc.gov	Jan 9, 2008	IVF; "assisted reproductive technologies"; "assisted reproductive techniques"; multiple AND (birth* or pregnancies OR gestation*) (five potentially relevant results)
Alberta Health and Wellness http://www.health.gov.ab.ca	Jan 9, 2008	IVF; in vitro fertilization; "assisted reproductive"; "assisted reproduction"; "multiple birth"; "multiple gestation"; Browsed list of publications as well (0 results)
Health Canada (http://www.hc-sc.gc.ca)	Jan 9, 2008	Looked at documents under Healthy living > Assisted human reproduction (http://www.hc-sc.gc.ca/hl-vs/reprod/index_e.html)
CDC – Centers for Disease Control and Prevention	Jan 9, 2007	Browsed through pages on Assisted Reproductive Technology (http://www.cdc.gov/ART/index.htm)

Database	Edition or date searched	Search Terms ††
US Medicare Coverage Database http://www.cms.hhs.gov/mcd/search.asp?		Keywords: IVF; in vitro fertilization; assisted reproduction; assisted reproductive
Aetna Clinical Policy Bulletins http://www.aetna.com/about/ cov_det_policies.htm	Jan 9 ,2007	In vitro fertilization
BlueCross BlueShield http://www.bluecares.com/		
Aggressive Research Intelligence Facility (ARIF) www.bham.ac.uk/arif		
TRIP Database http://www.tripdatabase.com		
Grey Literature		
NLH National Library for Health http://www.library.nhs.uk		
AETMIS http://www.aetmis.gouv.qc.ca		
CCOHTA http://www.ccohta.ca		
Institute for Clinical and Evaluative Sciences (ICES) http://www.ices.on.ca/		
ECRI (HTAIS Database) http://www.ecri.org		
Health Technology Assessment Unit At McGill http://www.mcgill.ca/tau/		
Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html		
NZHTA		
MHRA		
NICE		
Google http://www.google.com		

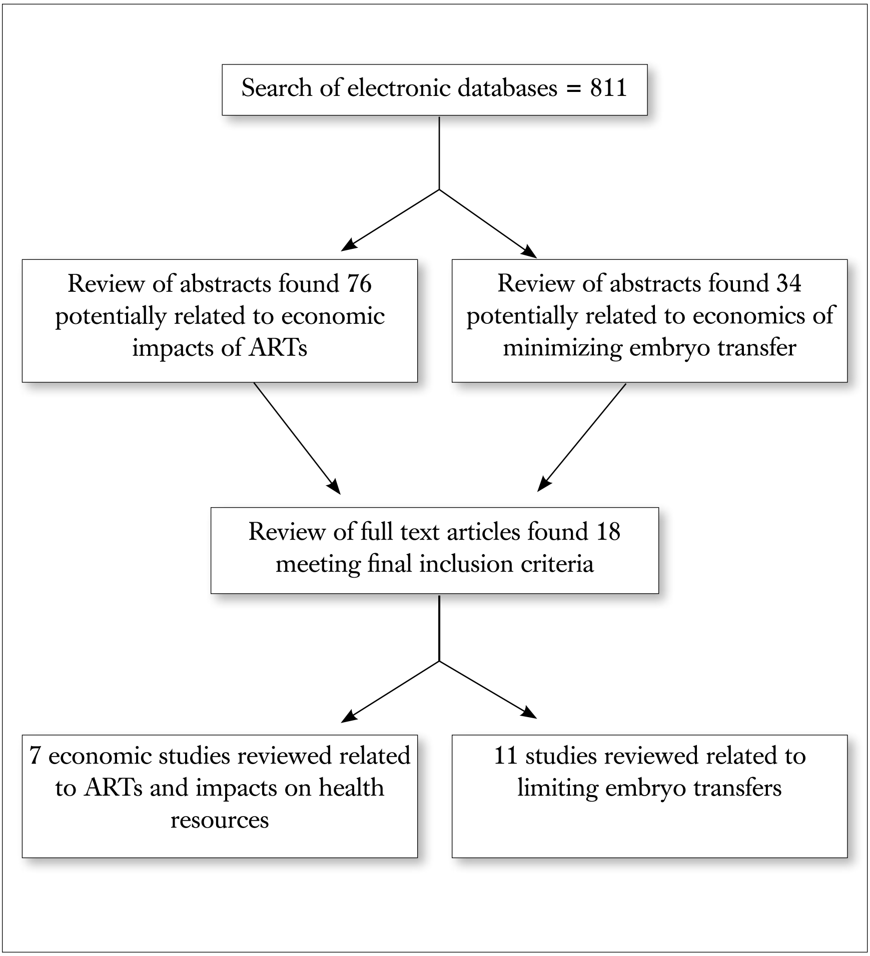
Note: † Limits: Searches were limited to publication dates ________; publication type: limited to __________ systematic reviews, etc,; language: English only; studies: human studies only. These limits are applied in databases where such functions are available.

†† "*", "# ", and "?" are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

Data Extraction

Extracted data from included studies were: place of origin, objective, evaluation type (e.g. costing or CEA), healthcare setting, timelines, study type (e.g. randomized controlled trial (RCT), perspective (e.g. societal or payer), costing methodology (e.g. healthcare services included, unit costs), unit of output (e.g. birth rate), study results, and study conclusion.

Progress through Selection of Potentially Relevant Studies



Appendix B: Summary of Studies Included in Review

Summary of Primary Studies of the Cost Impact of ARTs

Author / Country	Study Type	Objective / Perspective	Evaluation Type	Timeline
Koivurova et al. 2007[6] Finland	Retrospective Matched-Case Controlled Analysis	To compare post-neonatal hospital costs between IVF/ICSI births [singleton (n=153), twins (n=121), triplets (n=25), and quadruplets (n=4)] AND matched controls (n=567). Payer's Perspective	Costing (2004 £)	Birth to 7 years of age
Chambers et al. 2007[7] New Zealand	Retrospective Observational Study	To compare inpatient hospital costs between ARTs and non-ARTs: singletons (n=4050 vs 241,967), twins (n=1774 vs. 6398) and higher order multiples (n=62 vs 174) of both infants and their mothers. Payer's Perspective	Costing (1998-1999 €)	Birth to 5 years of age
Ledger et al 2006[8] The United Kingdom	DAM	To compare the cost of IVF singleton (n=4621), twin (n=1579) and triplet (n=109) pregnancies. Payer's Perspective.	Costing (2002 £)	Pregnancy to 1 year post delivery

Results	Study Conclusions	Evidence of Increased Health Care Costs
Overall IVF children had higher mean visits (1.76 vs. 1.07) and longer length of stay (4.31 vs. 2.61). IVF children cost 2.6 times more than general population based controls.	The incidence of multiple births increases the utilization of post-neonatal health care services and costs among IVF children in comparison to naturally conceived children.	Results suggest,that ARTs singletons are associated with higher hospital costs than natural singletons.
Compared to non-ARTs infants ARTs infants 4.4 and 5 times more likely to be low birth weight and very low birth weight respectively translating into 89% higher birth admissions costs (€2,832 vs. €1,502) Compared to non ARTs, maternal costs for ARTs singletons, twins and HOM were 11%, 6% & 8% higher than non ARTs respectively. Overall cost of all ART births was 57% higher than non-ART births.	Approximately €9.2 million could be saved in birth admissions alone if ART multiples had been singleton births. The authors conclude that the results highlight the need for policies supporting single embryo transfer.	Results suggest that ARTs with increased health care costs.
Total costs per IVF pregnancy were £3313 for singleton, £9122 for twin and £32,354 for triplet. Multiple pregnancies after IVF were linked with 56% of the cost, although they made up less than 1/3 of the total annual number of maternities.	Multiple pregnancies from IVF are associated with high costs to the health system. Savings could be made if the SET policy were adopted.	Because comparisons with non-IVF patients were not made, the costs directly attributable to ARTs are unclear. Results do not directly link ARTs with increased health care costs.

Summary of Primary Studies of the Cost Impact of ARTs (cont'd)				
Author / Country	**Study Type**	**Objective / Perspective**	**Evaluation Type**	**Timeline**
Koivurova et al 2004[10] Finland	Retrospective Observational Study	To compare the costs of IVF (n=215 mothers and 255 neonates) and natural conception (n=662 mothers and 388 neonates). Payer's Perspective	Costing (2003 €)	Prenatal and neonatal period
Cassell et al 2004[9] Nova Scotia Canada	Retrospective Observational Study	To compare the cost of singletons (n=113,222), twins (n=1724) and HOM (n=37) Payer's Perspective.	Costing (2002 CAD $)	Delivery to discharge
Lukassen et al. 2003[11] Netherlands	Retrospective Observational Study	To compare antenatal, delivery, and neonatal costs between singleton (n=135) and twin (n=144) pregnancies after receiving IVF. Payer's Perspective	Costing (2003 €)	Pregnancy to 6 weeks post delivery
Ericson et al. 2002[12] Sweden	Retrospective Observational Study	To compare hospital utilization between IVF singleton, twin and full term births. Payer's Perspective	Comparisons of Health Service Utilization From 1984-1997	Birth to 14 years of age
Little et al 2006[13] The USA	DAM	To compare direct and indirect health costs of transferring one through five embryos per IVF cycle (hypothetical cohort of 10,000). Patient, Insurer and Societal Perspective	Costing (2005 USA $)	Varied depending on perspective

Results	Study Conclusions	Evidence of Increased Health Care Costs
Prenatal and neonatal costs were €5,778.1 for IVF singletons, €4,495.6 for natural singletons, €15,579.5 for IVF twins and €14,447.7 for natural twins.	Multiple births increase the health care costs and therefore the reduction of multiple pregnancies is the most effective way to reduce the health care costs resulting from IVF.	Results suggest that ARTs is associated with increased health care costs.
Total hospital costs (maternal and neonatal) per pregnancy were $6750 for singletons, $39,430 for twins, $222,000 for triplets, and $278,400 for quadruplets. 51.4% of the HOM gestations were conceived through infertility therapy. HOM have longer LOS, are more likely to have cesarean delivery, preterm labor, preeclampsia, and require intensive care unit admission.	Maternal morbidity, perinatal morbidity/mortality, and hospital costs are significantly increased in higher order births. HOM	Results suggest that HOMs are associated with higher hospital costs.
Costs were €10,920 higher per twin pregnancy than per singleton pregnancy (€2549 vs. €13,469).	Reducing the number of twin pregnancies by implementing single embryo transfer will save costs.	Because comparisons with non-IVF patients were not made, the costs directly attributable to ARTs are unclear. Results do not directly link ARTs with increased health care costs.
Compared to non-IVF infants, singleton IVF infants had three more hospital stays than non-IVF infants. Compared to IVF singletons, IVF twins had 7.4 more hospital days (13 vs. 5.6).	Increased hospitalization of IVF children is largely attributable to multiple births. These costs may be reduced by single embryo transfers.	Results directly link ARTs with increased health care utilization.
SET was associated with the lowest total costs from the perspective of society and the third-party payer. DET or higher order transfer was the least expensive from a patient perspective. One-embryo transfers markedly improved clinical outcomes (e.g. preterm birth, low birth weight and cerebral palsy rate.)	SET is associated with the lowest health care costs from the perspective of society or the insurer.	Results indicate that SET is less costly than DET when incorporating both short and long term health and cost outcomes.

Summary of Cost Effectiveness Studies				
Author / Country	**Study Type**	**Objective / Perspective**	**Evaluation Type**	**Timeline**
Gerris et al. 2004[14] Belgium	Prospective Observational Study	To compare treatment, hospital and outpatient costs between patients receiving SET (n=206 women with good prognosis) and DET (n=161). Payer's Perspective	Costing (2000-2001€)	Pregnancy to three months post delivery
MAS[28] 2006 Ontario Canada	DAM	To evaluate the cost-effectiveness of IUI, 3 cycle SET-IVF and 3 cycle DET-IVF using fresh embryos (all 3 cycles) and frozen embryos (cycles 2 and 3).	CEA (2006 CAD$)	Admission for delivery to discharge
Fiddelers et al. 2006[16] Netherlands	RCT	To compare the cost effectiveness of SET (n=154) compared to DET (n=154). Societal Perspective	CEA (2003€) Effectiveness was defined as a successful live birth.	Initial IVF treatment to 4 weeks post delivery
Kjellberg et al. 2006[17] Sweden	RCT	To compare the cost effectiveness of SET + frozen embryo SET (n=330) compared to DET (n=331) in women younger than 37 years of age. Societal Perspective	CEA (2004€) Effectiveness was defined as a successful live birth.	Initial IVF treatment to 6 months post delivery

Results	Study Conclusions	Evidence of Cost Effectiveness
Total cost was €7,126 for SET with 37.4% resulting live births and €11,039 for DET with 36.6% resulting live births.	There is no difference in ongoing clinical pregnancy rate or live delivery rate between women with good prognosis receiving SET and women receiving DET.	Results directly link SET with lower cost.
Costs per live birth for: IUI = $21,000. SET (fresh)=$85,000 DET (fresh)=$33,000 SET (fresh & frozen) = $50,000 DET (fresh & frozen) = $28,000 Cost of providing coverage for IVF SET is approximately 9.8 to 12 million.	Costs of providing coverage for SET IVF exceeds the savings from reducing short term hospital and physician costs from reduced multiple births.	Cost effectiveness of SET is unclear due to study limitations.
SET costs = €7,334. DET costs = €10,924 SET pregnancy rate = 33.1% DET pregnancy rate = 40.3% ICER of DET= €19,096 per additional live birth.	In an unselective group of patients undergoing IVF treatment, SET is less expensive but also less effective compared with DET.	Cost effectiveness of SET is unclear due to study limitations.
SET costs = €3,069,989. DET costs = €4,077,155 SET pregnancy rate = 38.8% DET pregnancy rate = 42.9% ICER of DET= €91,702 per additional live birth.	In women younger than 37 years of age, DET is not cost effectiveness compared to SET.	Cost effectiveness of SET is unclear due to study limitations.

Summary of Cost Effectiveness Studies (cont'd)				
Author / Country	**Study Type**	**Objective / Perspective**	**Evaluation Type**	**Timeline**
De Sutter et al. 2002[18] Belgium	DAM	To compare the cost effectiveness of SET (n=1000 hypothetical women with good prognosis) to DET (n=1000 hypothetical cohort). Payer's Perspective	CEA (2001€) Effectiveness was defined as a successful live birth.	First embryo transfer to birth

SET – single embryo transfer DET – double embryo transfer ICER – incremental cost effectiveness ratio
RCT – randomized controlled trial DAM – decision analytic model

Results	Study Conclusions	Evidence of Cost Effectiveness
Cost per child calculations were not ICER between options. ICER = €11,805 per additional live birth for SET ICER = €10,966 per additional live birth for DET. Costs results were not reported separately.	More IVF cycles in SET are required to obtain the same number of children born in DET. However, because SET avoids twins there is no difference in the cost per child born between SET and DET.	Cost effectiveness of SET is unclear due to study limitations.

Appendix C: Distribution of Costs and Visits

The data analyses exclude extraneous costs and visits (i.e. outliers) that likely do not reflect the average costs/visits associated with birth plurality. The distribution and skew of the data was explored to determine the appropriate exclusion criteria for costs and visits. Final inclusion criteria were based on achieving parsimony between minimizing skew while maximizing sample size. Three potential exclusion criterions for trimming outliers were explored: trimming cases with costs/visits greater than 1, 2, or 3 times its standard deviation (SD).

Table B-1 compares the average hospital and physician costs for infants and mothers between the full data and after applying the three potential exclusion criterions. The degree of skewing was indicated by a "skewness" score in STATA 9.1. Negative values indicate the data is left-skewed while positive values indicate the data is right-skewed. Scores closer to zero indicate a more normal shaped distribution. Skew was minimal for mother's physician costs (skew = 1.26) and it was unnecessary to trim cases for mother's physician costs. However, the cost distribution for infant hospital costs, infant physician costs, and mother hospital costs were severely right-skewed. When applying an exclusion criterion of 1 and 2×SD, the degree of skew in the data was greatly minimized but also resulted in dropping many cases. It was determined that trimming outliers with 3×SD appropriately minimized skew while maximizing sample size. Figures B1 and B2 illustrate the scatterplot of hospital and physician costs for infants and mothers before and after applying the three exclusion criterions.

Table B-2 compares the average hospital and physician visits for infants and mothers between the full data and after applying the three potential exclusion criterions. Skew was minimal for all data except for infant physician visits. Applying an exclusion criterion of 1 or 2×SD to infant physician visits resulted in dropping 13,072 cases. It was determined that trimming outliers with 3×SD appropriately minimized skew while maximizing sample size. Figures B3 and B4 illustrate the scatterplot of hospital and physician visits for infants and mothers before and after applying the three exclusion criterions.

Table B-1: Hospital, physician, and total costs before and after trimming

Cost	N	Mean ($)	Std.Dev.	Min ($)	Max ($)	Skewness	Cases Dropped
Without Trimming Outliers							
Infant Hosp Cost	36,767	3845.57	15,795.72	14.37	791,350.00	15.17	—
Infant Phys Cost	36,767	684.29	1133.97	0.00	60,817.23	16.77	—
Total Infant Costs	36,767	4529.86	16,612.08	14.37	809,434.3	14.80	—
Mother Hosp Cost	36,158	3123.17	2984.19	34.00	122,910.00	11.03	—
Mother Phys Cost	36,158	2105.28	1040.98	0.00	16,588.65	1.26	—
Total Mother Costs	36,158	5228.45	3551.154	419	129,121.00	8.57	—
Trimming Outliers 1×SD							
Infant Hosp Cost	35,218	1733.86	2308.96	14.37	15,787.55	3.35	1549
Infant Phys Cost	32,935	481.89	240.42	0.00	1133.96	0.54	3832
Total Infant Costs	35,135	2259.30	2437.57	14.37	16,590.82	3.15	1632
Mother Hosp Cost	23,494	2031.21	535.77	34.00	2984.00	-0.61	12,664
Mother Phys Cost	3197	526.49	436.29	0.00	1046.42	-0.24	32,961
Total Mother Costs	9783	2847.826	532.2744	419	3551.13	-0.94	26,375
Trimming Outliers 2×SD							
Infant Hosp Cost	36,023	2179.72	3789.36	14.37	31,521.68	4.16	744
Infant Phys Cost	35,801	563.66	370.38	0.00	2265.97	1.61	966
Total Infant Costs	36,001	2750.30	4015.31	14.37	33,219.13	4.01	766
Mother Hosp Cost	33,964	2629.43	1083.18	34.00	5967.00	0.75	2194
Mother Phys Cost	20,389	1421.40	497.71	0.00	2092.95	-1.28	15,769
Total Mother Costs	30,744	4287.63	1294.52	419	7101.81	0.15	5414

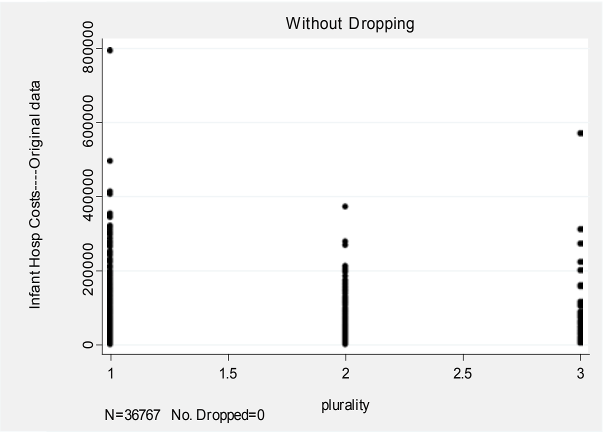
Trimming Outliers 3×SD							
Infant Hosp Cost	36,292	2450.07	4918.13	14.37	47,347.14	4.89	475
Infant Phys Cost	36272	591.5184	442.3182	0	3401.06	2.32	495
Total Infant Costs	36,278	3040.20	5204.92	14.37	49,629.14	4.76	489
Mother Hosp Cost	35,261	2792.08	1359.36	34.00	8951.00	1.41	897
Mother Phys Cost	31,182	1807.14	687.86	0.00	3139.51	-0.39	4976
Total Mother Costs	34,787	4758.86	1808.37	419	10,652.35	0.78	1371

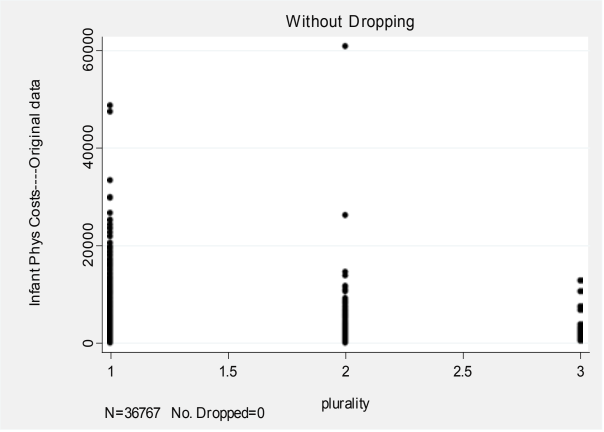
Table B-2: Hospital and physician visits for infants and mothers

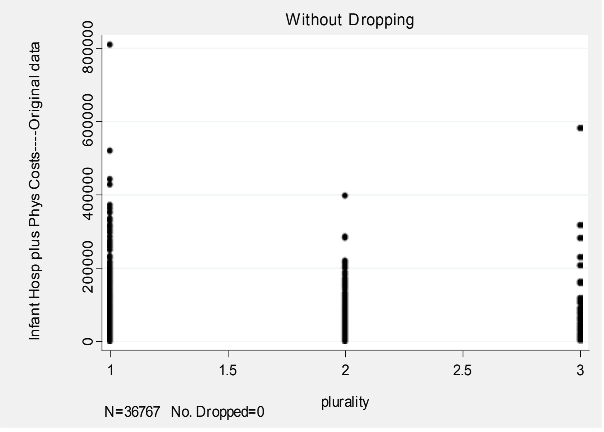
Cost	N	Mean ($)	Std.Dev.	Min ($)	Max ($)	Skewness	Cases Dropped
Without Trimming Outliers							
Infant Hosp Visits	36,767	1.20	0.63	1.00	15.00	5.91	—
Infant Phys Visits	36,767	13.37	13.17	0.00	779.00	17.12	—
Mother Hosp Visits	36,158	1.19	0.55	1.00	13.00	4.73	—
Mother Phys Visits	36,158	28.24	12.59	0.00	213.00	1.40	—
Trimming Outliers 1×SD							
Infant Hosp Visits	0	0.00	0.00	0.00	0.00	0.00	36,767
Infant Phys Visits	23,695	8.30	3.09	0.00	13.00	-0.43231	13,072
Mother Hosp Visits	0	0.00	0.00	0.00	0.00	0.00	36,158
Mother Phys Visits	2237	4.23	4.90	0.00	12.00	0.46	33,921

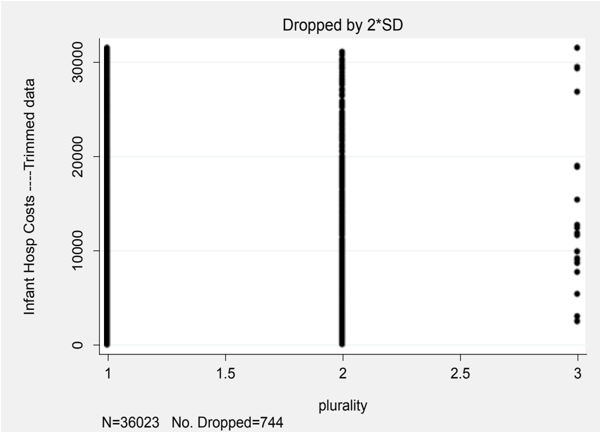
Trimming Outliers 2×SD							
Infant Hosp Visits	31,703	1.00	0.00	1.00	1.00	0.00	5064
Infant Phys Visits	34,380	11.32	5.50	0.00	26.00	0.51	2387
Mother Hosp Visits	31,135	1.00	0.00	1.00	1.00	0.00	5023
Mother Phys Visits	15,616	18.32	6.75	0.00	25.00	-1.55	20,542
Trimming Outliers 3×SD							
Infant Hosp Visits	31,703	1.00	0.00	1.00	1.00	0.00	5064
Infant Phys Visits	35988	12.2076	6.817009	0	39	1.09	779
Mother Hosp Visits	31,135	1.00	0.00	1.00	1.00	0.00	5023
Mother Phys Visits	29,936	24.24	8.21	0.00	37.00	-0.98	6222

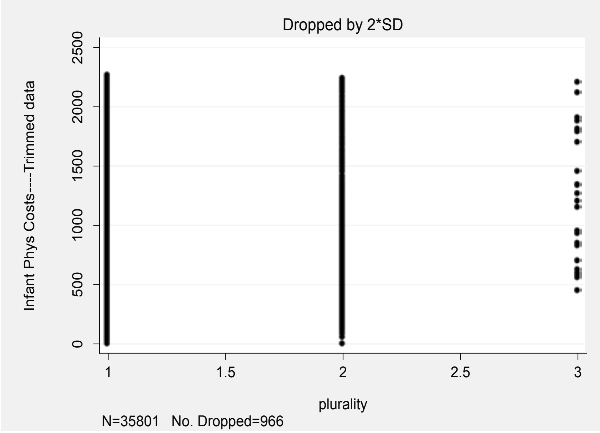
Figure B-1: Scatterplot of infant hospital and physician costs before and after trimming

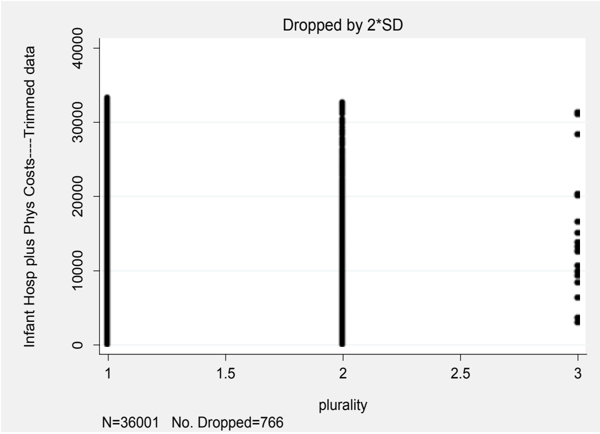


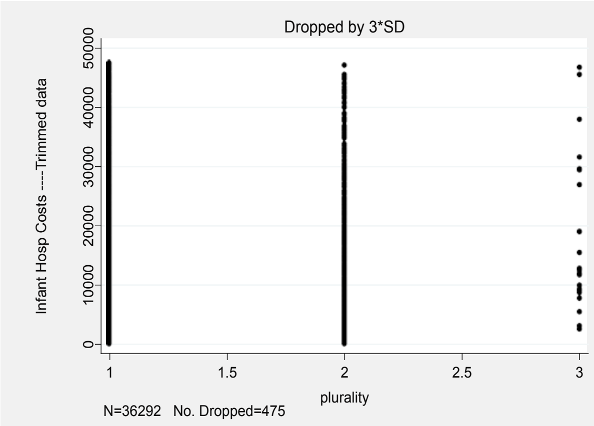


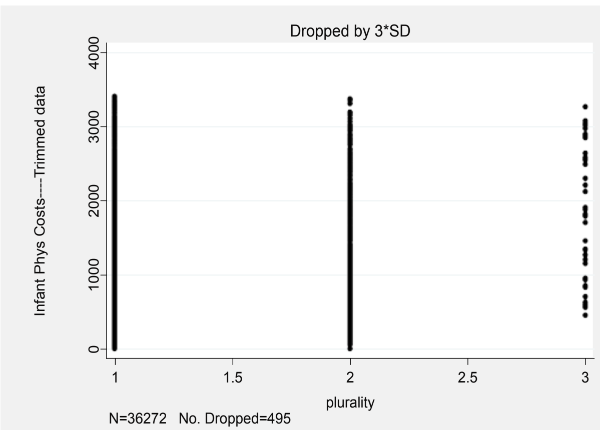



Dropped by 2*SD
Infant Hosp Costs ----Trimmed data
0
10000
20000
30000
1
1.5
2
2.5
3
plurality
N=36023 No. Dropped=744


Dropped by 2*SD
Infant Phys Costs----Trimmed data
0
500
1000
1500
2000
2500
1
1.5
2
2.5
3
plurality
N=35801 No. Dropped=966


Dropped by 2*SD
Infant Hosp plus Phys Costs----Trimmed data
0
10000
20000
30000
40000
1
1.5
2
2.5
3
plurality
N=36001 No. Dropped=766


Dropped by 3*SD
Infant Hosp Costs ----Trimmed data
0
10000
20000
30000
40000
50000
1
1.5
2
2.5
3
plurality
N=36292   No. Dropped=475


Dropped by 3*SD
Infant Phys Costs----Trimmed data
0
1000
2000
3000
4000
1
1.5
2
2.5
3
plurality
N=36272   No. Dropped=495

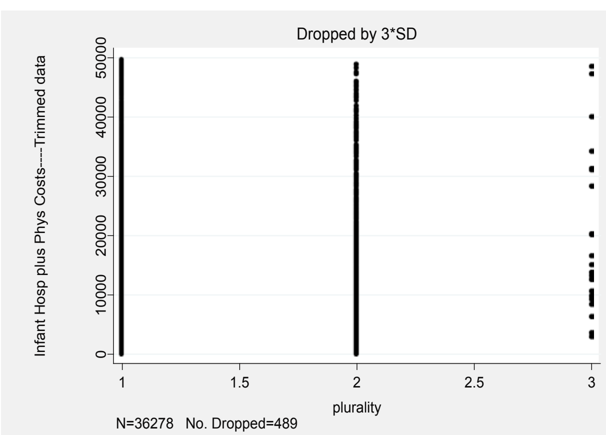
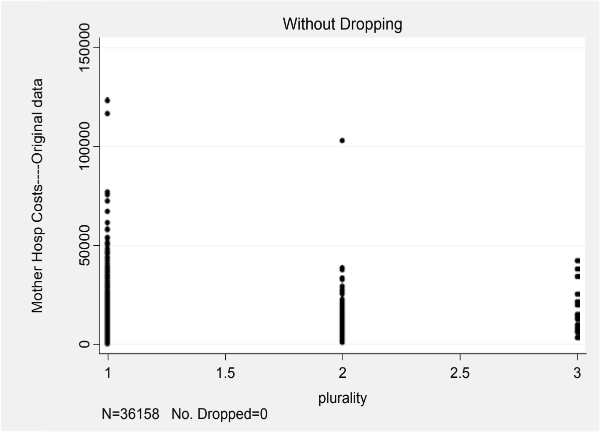
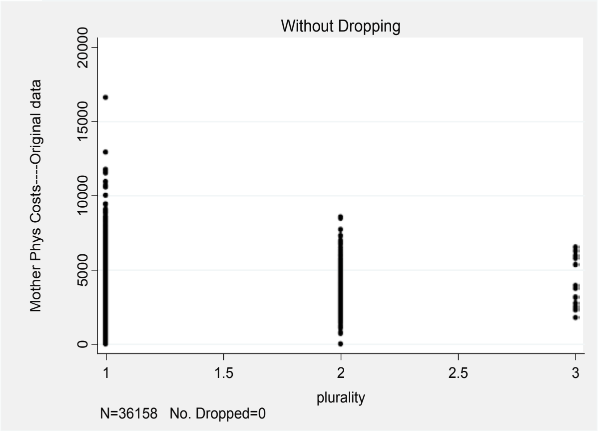
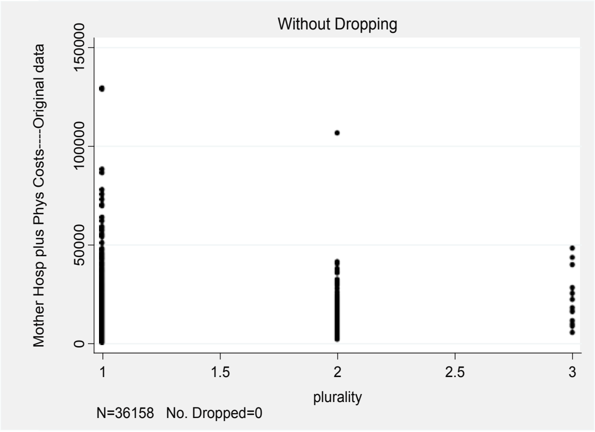
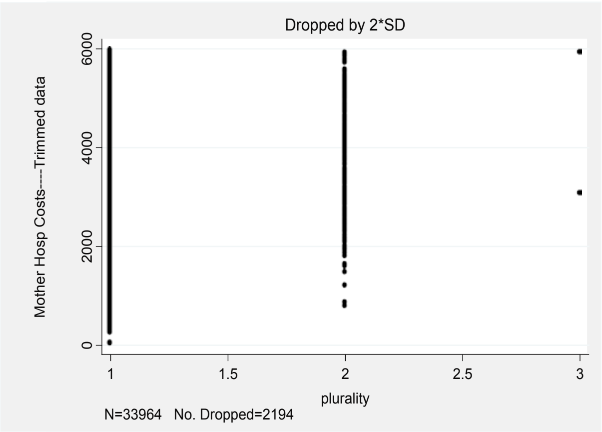

Dropped by 3*SD
Infant Hosp plus Phys Costs----Trimmed data
0
10000
20000
30000
40000
50000
1
1.5
2
2.5
3
plurality
N=36278   No. Dropped=489

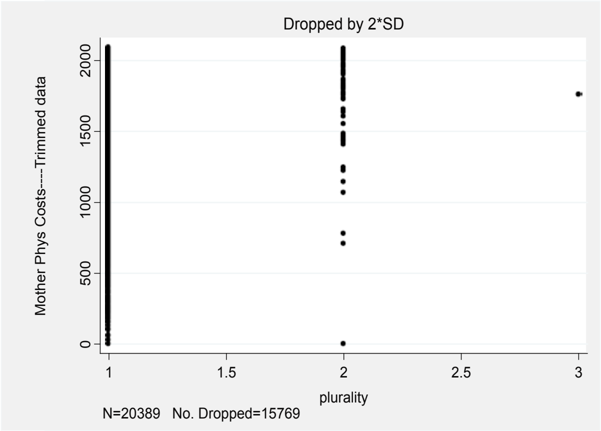
Figure B-2: Scatterplot of mother hospital and physician costs before and after trimming

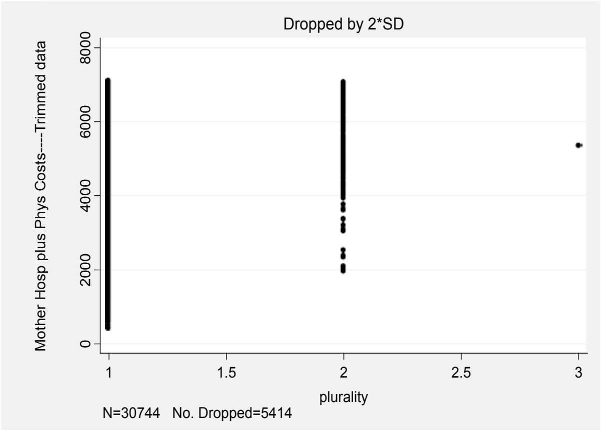


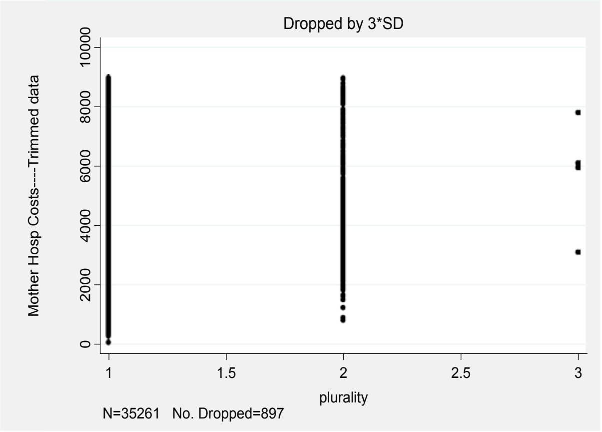


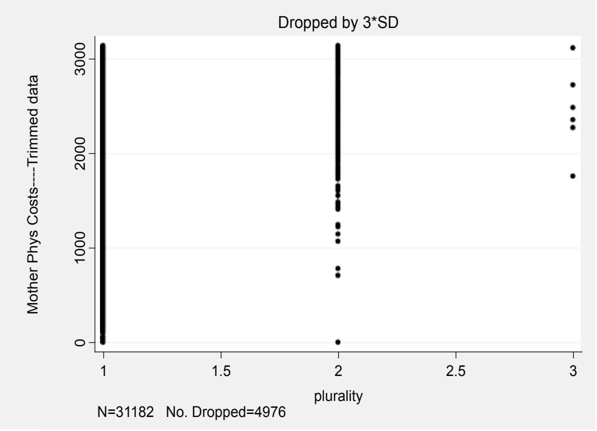



Dropped by 2*SD
Mother Hosp Costs----Trimmed data
0
2000
4000
6000
1
1.5
2
2.5
3
plurality
N=33964 No. Dropped=2194


Dropped by 2*SD
Mother Phys Costs----Trimmed data
0
500
1000
1500
2000
1
1.5
2
2.5
3
plurality
N=20389 No. Dropped=15769


Dropped by 2*SD
Mother Hosp plus Phys Costs----Trimmed data
0
2000
4000
6000
8000
1
1.5
2
2.5
3
plurality
N=30744 No. Dropped=5414


Dropped by 3*SD
Mother Hosp Costs----Trimmed data
0
2000
4000
6000
8000
10000
1
1.5
2
2.5
3
plurality
N=35261 No. Dropped=897


Dropped by 3*SD
Mother Phys Costs----Trimmed data
0
1000
2000
3000
1
1.5
2
2.5
3
plurality
N=31182 No. Dropped=4976

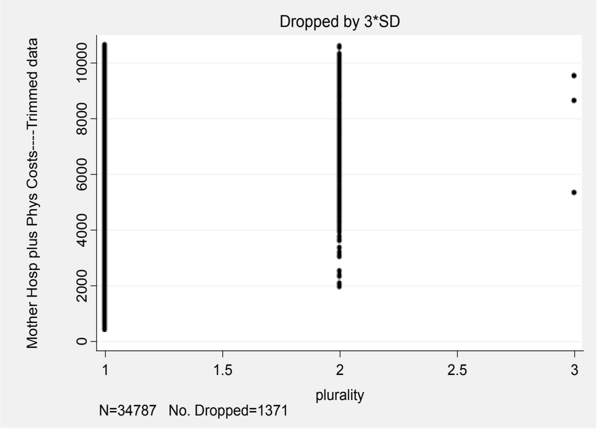
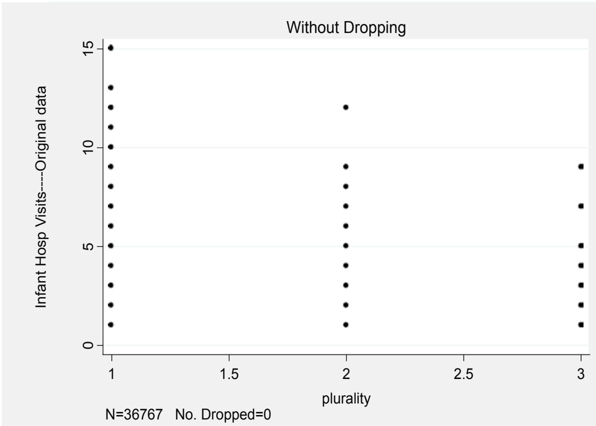
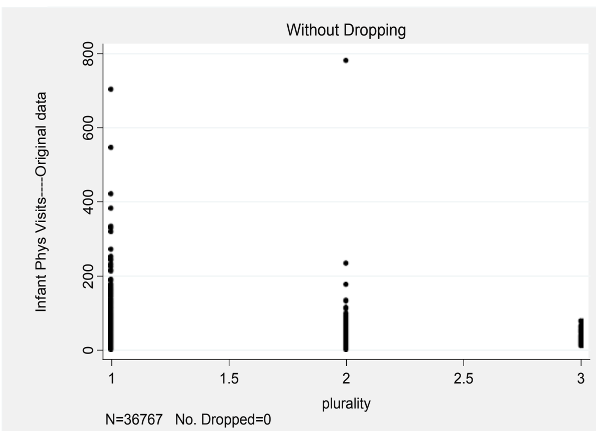
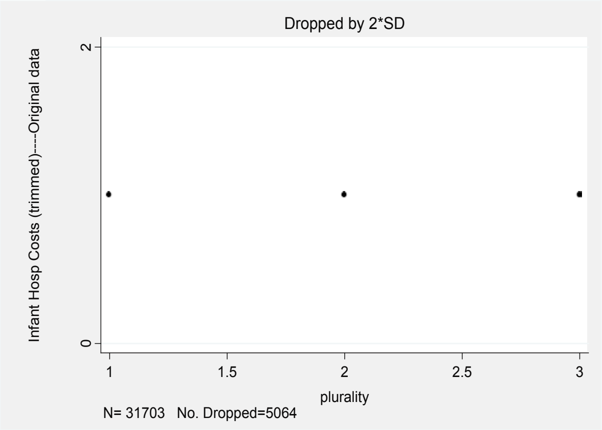
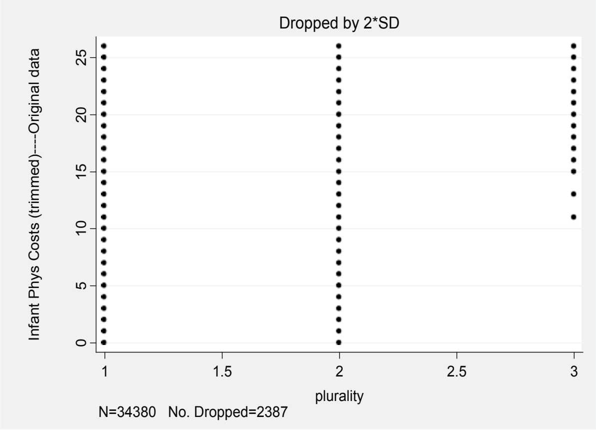

Dropped by 3*SD
Mother Hosp plus Phys Costs----Trimmed data
0
2000
4000
6000
8000
10000
1
1.5
2
2.5
3
plurality
N=34787 No. Dropped=1371

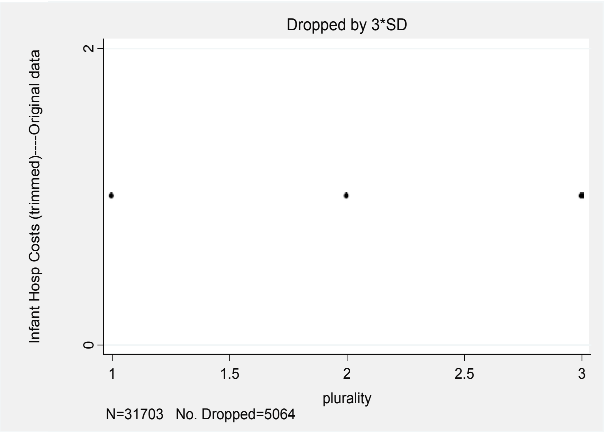
Figure B-3: Scatterplot of infant hospital and physician visits before and after trimming



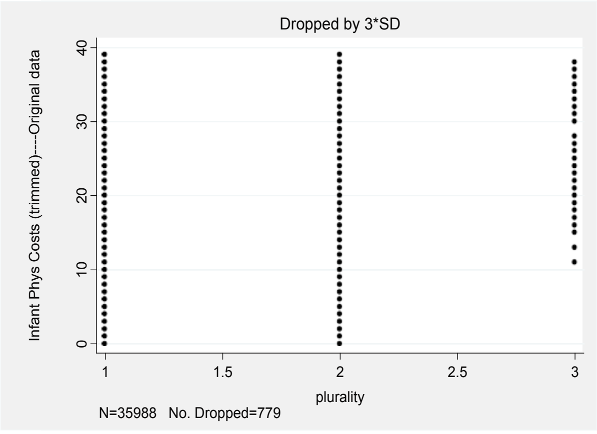



Dropped by 2*SD
Infant Hosp Costs (trimmed)----Original data
2
0
1
1.5
2
2.5
3
plurality
N= 31703   No. Dropped=5064


Dropped by 2*SD
Infant Phys Costs (trimmed)----Original data
25
20
15
10
5
0
1
1.5
2
2.5
3
plurality
N=34380   No. Dropped=2387

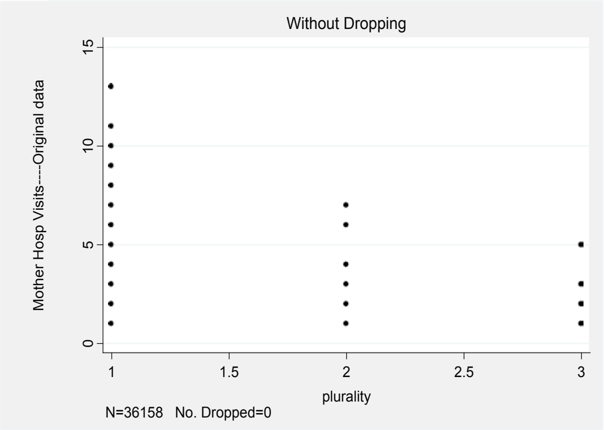


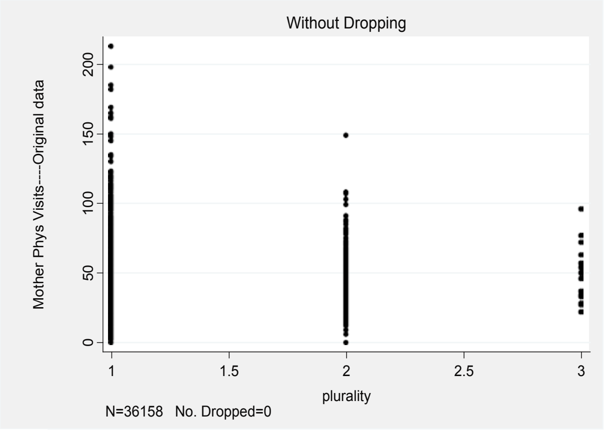
Dropped by 3*SD
Infant Hosp Costs (trimmed)----Original data
2
0
1
1.5
2
2.5
3
plurality
N=31703 No. Dropped=5064

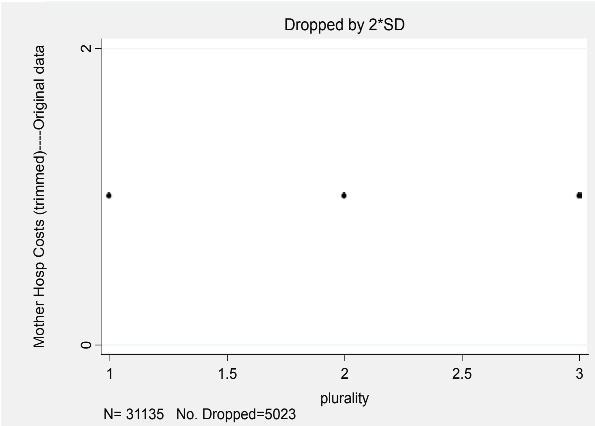


Dropped by 3*SD
Infant Phys Costs (trimmed)----Original data
40
30
20
10
0
1
1.5
2
2.5
3
plurality
N=35988 No. Dropped=779

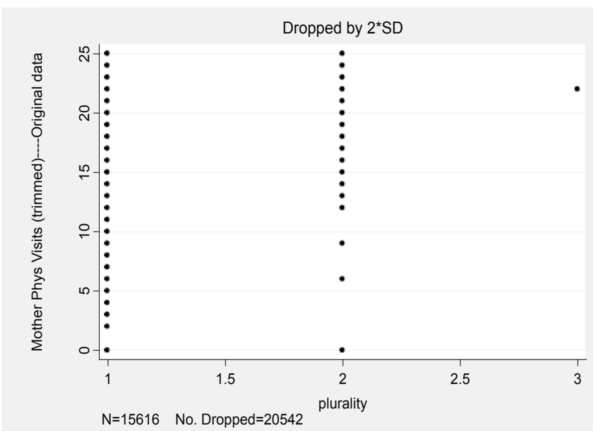
Figure B-4: Scatterplot of mother hospital and physician visits before and after trimming



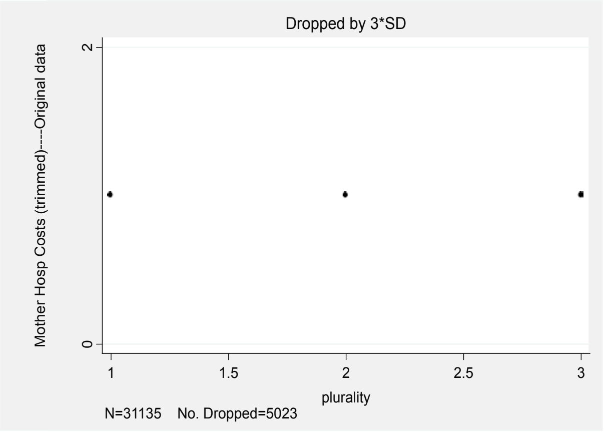


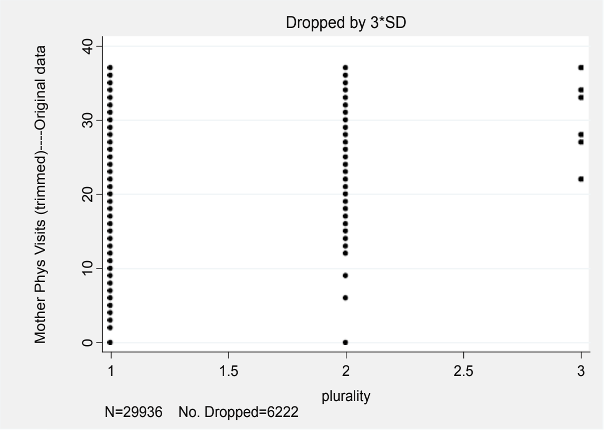


Dropped by 2*SD
Mother Hosp Costs (trimmed)---Original data
2
0
1
1.5
2
2.5
3
plurality
N= 31135 No. Dropped=5023



Dropped by 2*SD
Mother Phys Visits (trimmed)---Original data
25
20
15
10
5
0
1
1.5
2
2.5
3
plurality
N=15616 No. Dropped=20542


Dropped by 3*SD
Mother Hosp Costs (trimmed)---Original data
2
0
1
1.5
2
2.5
3
plurality
N=31135 No. Dropped=5023


Dropped by 3*SD
Mother Phys Visits (trimmed)---Original data
40
30
20
10
0
1
1.5
2
2.5
3
plurality
N=29936 No. Dropped=6222

Appendix D: Linear Regression Models

Regression Models of Costs for Infants						
Infant Hosp Costs (Full Data)	N=36,767 R-squared = 0.1517					
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin (ref Singleton)	2375.17	583.66	4.07	0.00	1,231.19	3,519.15
HOM (ref Singleton)	14,848.91	10,287.99	1.44	0.15	-5,315.85	35,013.66
Birth Weight (ref NBW)	22,971.38	364.60	63.00	0.00	22,256.76	23,686.00
Twin × Birth Weight	-1992.93	907.57	-2.20	0.03	-3,771.79	-214.07
HOM × Birth Weight	41,603.50	10,530.53	3.95	0.00	20,963.37	62,243.64
Constant	2289.67	79.11	28.94	0.00	2,134.62	2,444.73
Infant Physician Costs (Full Data)	N=36,767 R-squared = 0.0609					
Twin (ref Singleton)	269.56	44.09	6.11	0.00	183.14	355.97
HOM (ref Singleton)	567.51	777.12	0.73	0.47	-955.67	2,090.69
Birth Weight (ref NBW)	1158.59	27.54	42.07	0.00	1,104.61	1,212.57
Twin × Birth Weight	-420.05	68.55	-6.13	0.00	-554.42	-285.68
HOM × Birth Weight	417.83	795.44	0.53	0.60	-1,141.27	1,976.92
Constant	608.16	5.98	101.78	0.00	596.45	619.88
Infant total Costs (Full Data)	N=36,767 R-squared = 0.1497					
Twin (ref Singleton)	2644.72	614.57	4.30	0.00	1440.15	3849.30
HOM (ref Singleton)	15416.41	10832.91	1.42	0.16	-5816.39	36649.22
Birth Weight (ref NBW)	24129.97	383.91	62.85	0.00	23377.49	24882.44
Twin × Birth Weight	-2412.99	955.64	-2.52	0.01	-4286.07	-539.91
HOM × Birth Weight	42021.33	11088.29	3.79	0.00	20287.96	63754.70
Constant	2897.84	83.30	34.79	0.00	2734.57	3061.11

Note. Skew was assessed separately for hospital costs, physician costs and total costs. Refer to Appendix B for further details.

Variable Codings:

LBW = 1 & NBW = 0; Twin = 1 & 0 otherwise (ref is singleton); HOM = 1 & 0 otherwise (ref is singleton); Twin × Birth weight = 1 for the Twin and LBW and 0 otherwise; HOM × Birth weight = 1 for HOM & LBW and 0 otherwise.

Infant Hosp Costs (Excluding Outliers)	N=36,292 R- squared = 0.2294					
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin (ref Singleton)	1506.811	174.1613	8.65	0	1165.45	1848.173
HOM (ref Singleton)	15277.06	3053.085	5	0	9292.923	21261.2
Birth Weight (ref NBW)	9884.229	116.3785	84.93	0	9656.123	10112.33
Twin × Birth Weight	-79.3278	281.6209	-0.28	0.778	-631.313	472.6574
HOM × Birth Weight	-8852.99	3197.188	-2.77	0.006	-15119.6	-2586.41
Constant	1861.52	23.52288	79.14	0	1815.415	1907.626
Infant Phys Costs	N=36,272 R-squared =0.0993					
Twin (ref Singleton)	100.7971	17.01472	5.92	0	67.44771	134.1464
HOM (ref Singleton)	619.6725	296.8556	2.09	0.037	37.82686	1201.518
Birth Weight (ref NBW)	564.9452	11.06822	51.04	0	543.2512	586.6393
Twin × Birth Weight	-58.711	27.10983	-2.17	0.03	-111.847	-5.57497
HOM × Birth Weight	150.8492	304.9649	0.49	0.621	-446.891	748.5895
Constant	556.0025	2.291143	242.67	0	551.5118	560.4932
Infant Total Costs	N=36,278 R-squared = 0.2245					
Twin (ref Singleton)	1527.679	185.1944	8.25	0	1164.692	1890.665
HOM (ref Singleton)	15888.95	3241.394	4.9	0	9535.72	22242.18
Birth Weight (ref NBW)	10369.82	123.6812	83.84	0	10127.4	10612.23
Twin × Birth Weight	-69.5658	299.3533	-0.23	0.816	-656.307	517.1754
HOM × Birth Weight	-9247.45	3394.39	-2.72	0.006	-15900.6	-2594.34
Constant	2425.307	24.9767	97.1	0	2376.352	2474.262

Regression Models of Costs for Mothers						
Infant Hosp Costs (Full Data)	**N=36,158 R-squared = 0.0674**					
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin or HOM (ref. singleton)	2023.55	181.5603	11.15	0	1667.687	2379.414
Birth Weight	2772.793	72.25404	38.38	0	2631.173	2914.413
Twin or HOM × Birth Weight	737.4499	267.5469	2.76	0.006	213.0501	1261.85
Constant	2942.344	15.66998	187.77	0	2911.63	2973.058
Infant Physician Costs (Full Data)	**N=36,158 R-squared = 0.0249**					
Twin or HOM (ref. singleton)	1064.067	64.61881	16.47	0	937.4124	1190.722
Birth Weight	332.3077	25.71581	12.92	0	281.904	382.7115
Twin or HOM × Birth Weight	75.38398	95.22216	0.79	0.429	-111.254	262.0222
Constant	2072.267	5.577076	371.57	0	2061.336	2083.198
Infant total Costs (Full Data)	**N=36,158 R-squared = 0.0671**					
Twin or HOM (ref. singleton)	3,087.62	215.98	14.30	-	2,664.29	3,510.94
Birth Weight	3,105.10	85.95	36.13	-	2,936.63	3,273.57
Twin or HOM × Birth Weight	812.83	318.27	2.55	0.01	189.02	1,436.65
Constant	5,014.61	18.64	269.02	-	4,978.08	5,051.15

Note. Skew was assessed separately for hospital costs, physician costs and total costs. Refer to Appendix B for further details. Twins and HOM were combined because there were no HOM that were of NBW (i.e. could not construct interaction terms separately for HOM and therefore HOM were combined with twins). [a]No trimming was conducted on mother's physician costs.

Variable Codings:

LBW = 1 & NBW = 0; Twin or HOM = 1 & 0 otherwise (ref is singleton); Twin or HOM × Birth Weight = 1 for Twin or HOM and LBW and 0 otherwise.

Infant Hosp Costs (Excluding Outliers)	N=35,261 R-squared =0.0371					
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin or HOM (ref. singleton)	1371.058	87.14047	15.73	0	1200.259	1541.856
Birth Weight	967.7722	36.2422	26.7	0	896.7364	1038.808
Twin or HOM × Birth Weight	-292.21	136.1062	-2.15	0.032	-558.982	-25.4371
Constant	2733.472	7.296029	374.65	0	2719.172	2747.773
Infant Phys Costs	**N=36,158 R-squared = 0.0249**					
Twin or HOM (ref. singleton)	a	a	a	a	a	a
Birth Weight	a	a	a	a	a	a
Twin or HOM × Birth Weight	a	a	a	a	a	a
Constant	a	a	a	a	a	a
Infant Total Costs	**N=34,787 R-squared = 0.0276**					
Twin or HOM (ref. singleton)	2012.187	122.2992	16.45	0	1772.476	2251.897
Birth Weight	1038.534	49.22024	21.1	0	942.0611	1135.008
Twin or HOM × Birth Weight	-530.036	196.905	-2.69	0.007	-915.976	-144.096
Constant	4694.948	9.808238	478.67	0	4675.724	4714.173

Regression Models of Visits for Infants						
Infant Hosp Visits (Full Data)	N=36,767 R-squared =0.0387					
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin or HOM (ref. singleton)	0.089	0.02	3.59	0	0.040	0.137
Birth Weight	0.835	0.44	1.91	0.056	-0.022	1.691
Twin or HOM × Birth Weight	0.514	0.015	33.23	0	0.484	0.545
Constant	-0.183	0.039	-4.75	0	-0.258	-0.107
Infant Physician Visits (Full Data)	N=36,767 R-squared =0.0509					
Twin or HOM (ref. singleton)	2.34	0.51	4.55	0.00	1.33	3.35
Birth Weight	3.94	9.07	0.43	0.66	-13.85	21.72
Twin or HOM × Birth Weight	12.63	0.32	39.29	0.00	12.00	13.26
Constant	-4.50	0.80	-5.63	0.00	-6.07	-2.93

Note. Skew was assessed separately for hospital visits, physician visits and total visits. Refer to Appendix B for further details.
[a]No trimming was conducted on infant hospital visits.

Variable Codings:

LBW = 1 & NBW = 0; Twin = 1 & 0 otherwise (ref is singleton); HOM = 1 & 0 otherwise (ref is singleton); Twin × Birth weight = 1 for the Twin and LBW and 0 otherwise; HOM × Birth weight = 1 for HOM & LBW and 0 otherwise.

Infant Hosp Visits (Excluding Outliers)						
Variable	Coef.	SE	t	P>t	[95% Conf. Interval]	
Twin or HOM (ref. singleton)	a	a	a	a	a	a
Birth Weight	a	a	a	a	a	a
Twin or HOM × Birth Weight	a	a	a	a	a	a
Constant	a	a	a	a	a	a
Infant Phys Visits		**N=35,988 R-squared =0.0347**				
Twin or HOM (ref. singleton)	0.433	0.273	1.59	0.112	-0.1013	0.9683
Birth Weight	4.601	4.7363	0.97	0.331	-4.6823	13.885
Twin or HOM × Birth Weight	5.309	0.1813	29.32	0	4.9543	5.664
Constant	-0.329	0.4393	-0.75	0.453	-1.1903	0.531

Regression Models of Visits for Mothers						
Mother Hosp Visits **R-squared =0.0161**					N=36,158	
Variable	Coef.	Std. Err.	t	P>t	[95% Conf. Interval]	
Twin or HOM (ref. singleton)	0.156351	0.034322	4.56	0	0.08908	0.223623
Birth Weight	0.287033	0.013659	21.01	0	0.260261	0.313804
Twin or HOM × Birth Weight	-0.02785	0.050576	-0.55	0.582	-0.12698	0.071286
Constant	1.169139	0.002962	394.68	0	1.163333	1.174945
Mother Phys Visits **R-squared =0.0167**					N=361,58	
Twin or HOM (ref. singleton)	9.340605	0.784762	11.9	0	7.802448	10.87876
Birth Weight	3.66251	0.312305	11.73	0	3.050383	4.274638
Twin or HOM × Birth Weight	1.872468	1.156424	1.62	0.105	-0.39416	4.139092
Constant	27.89861	0.067731	411.9	0	27.76586	28.03137

Note. Skew was assessed separately for hospital visits, physician visits and total visits. Refer to Appendix B for further details. No cases were excluded for hospital or physician visits.

Variable Codings:

LBW = 1 & NBW = 0; Twin or HOM = 1 & 0 otherwise (ref is singleton); Twin or HOM × Birth Weight = 1 for Twin or HOM and LBW and 0 otherwise.

Appendix E: Sensitivity Analysis Results

Table E-1 contrasts the linear cost predictions (i.e. the results presented in Figure 2-A) for infants with and without excluding outliers. For infant costs, excluding outliers significantly reduced costs. Hospital costs for LBW infants were the most affected with a reduction in costs ranging from $13,515 for singletons to $63,544 for HOM. It is noteworthy to mention that for NBW HOM the difference in costs is zero. This is explained by the fact that there are very few cases that were NBW HOM and hence no cases were remaining after excluding outliers.

Table E-2 contrasts the linear cost predictions (i.e. the results presented in Figure 2-B) for mothers with and without excluding outliers. For mother costs, excluding outliers also reduced costs. Hospital costs for mothers with LBW infants were most affected with a reduction in costs ranging from $2014 for singletons to $3696 for ≥ twins. There were no cases excluded for mother's physician costs.

Table E-1: Infant costs with and without excluding outliers

Birth Weight	Excluding Outliers			Entire Sample Population			Difference		
	Singleton	Twin	HOM	Singleton	Twin	HOM	Singleton	Twin	HOM
Hospital Costs									
NBW	1862	3368	17,139	2290	4665	17,139	428	1297	0
LBW	11,746	13,173	18,170	25,261	25,643	81,713	13,515	12,470	63,544
Physician Costs									
NBW	556	657	1176	608	878	1176	52	221	0
LBW	1121	1163	1891	1767	1616	2752	646	453	861

Note: Skew was assessed separately for hospital costs and physician costs. Refer to Appendix C for further details.
Hosp (Full Data): N=36,767 R-squared = 0.1517 Hosp (Excluding): N=36,292 R-squared =0.2294
Phys (Full Data): N=36,767 R-squared = 0.0609 Phys (Excluding): N=36,272 R-squared =0.0993

Table E-2: Mother's costs with and without excluding outliers

Birth Weight	Excluding Outliers		Entire Sample Population		Difference	
	Singleton	Twin + HOM	Singleton	Twin + HOM	Singleton	Twin + HOM
Hospital Costs						
NBW	2733	4105	2942	4966	209	861
LBW	3701	4780	5715	8476	2014	3696

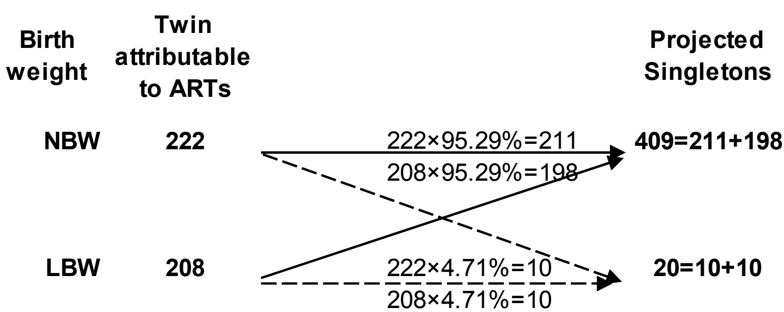
a. No cases were excluded for mother physician costs. Skew was assessed separately for hospital costs and physician costs. Refer to Appendix C for further details.

Hosp (Full Data): N=36,158 R-squared =0.0674 Hosp (Excluding): N=35,261 R-squared =0.0371

Appendix F: Calculation of Savings had Twins/HOM been Singletons

The available data did not identify which pregnancies resulted from ARTs procedures. Consequently, estimating the health services cost attributable to ARTs from the AHW data and conversely estimating the amount of costs that can potentially be minimized had ARTs twins and HOM been singleton pregnancies, requires an assumption regarding the proportion of twins and HOM birth events attributable to ARTs procedures.

It is important to recognize, however, that there are a small proportion of singleton infants that are born with LBW. To increase the validity of estimating potential savings, the cost calculation needed to account for the proportion of twins and HOM that would still have been born a singleton LBW infant. Based on the administrative cost data, 95.29% and 4.71% of infants were born with NBW and LBW, respectively (shown in Table 2-B). The analysis therefore assumes that had ARTs twins and HOM been singletons, 95.29% and 4.71% would have been of NBW and LBW, respectively. The figure below provides an illustration of the calculation.



Mapping Twins to Singletons

The proportion of twins and HOM attributable to ARTs were 35% and 77%, respectively.[26] Applying these figures to the number of twins and HOM in the dataset (shown in Table 2-B), Table F-1 shows the number of twins and HOM assumed to be attributable to ARTs and of these, the number of infants that could have been a singleton infant further subdivided by birth weight.

Total health services costs of twins and HOM in the data set are estimated by multiplying the number of ARTs twins and HOM by their respective linear prediction of total costs shown in Figure 2-A (for infant costs) and Figure 2-B (for mother costs) (Current Scenario). Alternatively, the total health care costs had twins and HOM been singletons instead, are estimated by multiplying the number of projected ARTs singletons by their respective linear prediction of total costs shown in Figure 2-A (for infant costs) and Figure 2-B (for mother costs) (Alternative Scenario). Hence, the amount of savings to the health care system is the difference between the Current and Alternative scenario.

Table F-1: Projected singletons

Birth weight	Number of Twins[a]	Twins Attributable to ARTs[b]	Projected Singletons[c]	Number of HOM[a]	HOMs Attributable to ARTs[d]	Projected Singletons[c]	Total Projected Singletons
Infants							
NBW	633	222	409	2	2	33	442
LBW	594	208	20	43	33	2	22
Mothers							
NBW	234	89	163	0	0	10	173
LBW	255	82	8	14	11	1	9

a. Values are taken from Table 2-B.

b. Assume 35% are attributable to ARTs.[26]

c. Based on 95.29% and 4.71% of singletons in the data being NBW and LBW respectively. Refer to Appendix F for details on the mapping of twins and HOM into singletons.

d. Assume 77% are attributable to ARTs.[26]

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