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ORIGINAL ARTICLE

Impact of ART on pregnancies in California: an analysis of maternity outcomes and insights into the added burden of neonatal intensive care

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OBJECTIVE: We reviewed the occurrence of prematurity, low birth weight, multiple gestations, frequency of stillbirths and maternity care-associated variables including hospital stay and hospital charges of women conceiving using assisted reproductive technology (ART) or artificial insemination (AI) compared with women with a history of infertility who conceived naturally, and all other naturally conceived pregnancies in California at non-federal hospitals between 2009 and 2011. At a single center, infants born after ART/AI were compared with infants provided care in the normal nursery.

STUDY DESIGN: Publically available inpatient data sets from the California Office of Statewide Health Planning and Development for years 2009–2011 using data from all California non-federal hospitals were used to determine the impact of ART on a variety of pregnancy-related outcomes and infant characteristics. Infant data from a single center was used to determine hospital charges for infants delivered over an 18-month period to compare the hospital and physician charges indexed to similar charges for infants admitted to the 'normal' newborn nursery.

RESULT: Among ART/AI pregnancies, there was a 4–5-fold increase in stillbirths, compared with a 2–3-fold increase among women with infertility compared with other naturally conceiving women. ART/AI pregnancies underwent more cesarean sections (fourfold), and a near fourfold increase in the rate of preterm deliveries. Multiple gestations were increased 24–27-fold compared with naturally conceived pregnancies. Maternal hospital stay and hospital charges were increased among those undergoing ART/AI. Infant charges were increased multi-fold for singletons, twins and triplets delivered after ART/AI compared with naturally conceived infants.

CONCLUSION: Multiple births, preterm births and a higher overall rate of fetal anomalies were found in California after ART/AI for 2009–2011. Cesarean section rates, longer length of maternal stay and hospital charges among women receiving ART/AI could be lowered if emphasis on elective single embryo transfers was a higher priority among providers. Charges for the care of infants delivered after ART/AI are substantially higher than among naturally conceived infants born late preterm or at term. Families seeking ART/AI need to be informed of the impact of these adverse pregnancy outcomes, including neonatal outcomes and charges for medical care for their infant(s), when considering ART/AI.

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Keywords: assisted reproductive technologies; maternal morbidity; multiple gestations; low birth weight infant; NICU charges; embryo transfer

INTRODUCTION

Infertility affects ~7.4% of married couples in the United States.[1] The causes of infertility are multiple. Treatments for infertility have included ovarian stimulation, reconstruction surgery after previous tubal ligation or vasectomy and intrauterine insemination. Since 1978 in the UK and 1981 in the United States, the use of assisted reproductive technologies (ARTs) has assisted infertile couples achieve pregnancy.[2,3] In 2009, there were 146 244 ART procedures (primarily *in vitro* fertilization) performed in the United States as reported to the Centers for Disease Control and Prevention, of which the largest number occurred in California (18 405).[4] About 1.4% of U.S. births in 2009 resulted from ART, with the state of Massachusetts reporting the highest proportion of births resulting from ART (4.3%). In California, 1.4% or 7545 of 527 020 live-born infants resulted from ART, of which only 52.7% were singletons compared with 96.8% of all naturally conceived infants.[4]

We reviewed the incidence of various morbidities including prematurity, low birth weight infants, multiple gestations and stillbirths in pregnancies conceived using ART/artificial insemination (AI). We also reviewed the potential impact of these services on the costs attributable to maternity care, and hospital and physician charges at our center. We sought to establish baseline data and to understand the implications of wide availability of these reproductive services that may occur with health-care reform. Although Massachusetts, Michigan, Florida and Connecticut have participated in the States Monitoring Assisted Reproductive Technology Collaborative from the Centers for Disease Control and Prevention, which includes specific demographics regarding ART in these states, California data are not included in this database.[5] Publicly available inpatient discharge data sets from the California OSHPD (Office of Statewide Health Planning and Development) for years 2009–2011 were used to extrapolate

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the impact of ART on a variety of pregnancy-related outcomes by comparing three groups of delivering mothers: women using ART/AI, women with a diagnosis of infertility in whom such services were not used and all other women delivering babies each year. We also examined hospital and physician charges for infants delivered after ART/AI procedures at a single center.

We hypothesized that pregnancies conceived by ART or AI would be at higher risk for adverse pregnancy-associated outcomes, and that by identification of these outcomes, greater focus might redirect health-care resources toward improving the outcomes of these pregnancies. The cost of neonatal care for infants delivered after conception using ART/AI during 2012 and the first 6 months of 2013 was tabulated from a large Southern California medical center with ART services provided by this medical center and from other fertility centers.

METHODS

This retrospective study was performed after obtaining institutional research board approval from Loma Linda University. Public versions of the 2009–2011 Patient Discharge Data Files from California OSHPD were used to estimate the impact of ART and infertility on a variety of pregnancy-related outcomes. This annual data set contains a unique record for every inpatient discharge from all non-federal hospitals licensed in California. A discharge abstract is reported for each inpatient hospitalization and includes, among other things, patient demographics, admission and discharge details and International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes specific to the patient of record.[6] Discharge records were identified as maternal delivery discharges if they met all of the following criteria: Major Diagnostic Category (MDC) equal to Pregnancy, Childbirth, and the Puerperium,[6] Medicare Severity-Diagnosis Related Group (MS-DRG) equal to cesarean delivery (765, 766) or vaginal delivery (767, 768, 774, 775); and an Outcome of Delivery ICD-9-CM code (V27) among any of 25 diagnosis fields available in the data set. Maternal delivery discharges were then assigned to one of three mutually exclusive groups: ART/AI, infertility or natural conception. Discharges were assigned to the ART/AI group if either of the following ICD-9-CM codes was present in the record: V23.85 – pregnancy resulting from ART or V26.1 –AI. The infertility group consisted of women whose records did not include an ART or AI ICD-9-CM code but did include either of the following: 628 – infertility (female), or V23.0 – pregnancy with history of infertility. All other maternal delivery discharges were assigned to the natural conception group. Diagnosis fields were further queried for incidence of the following pregnancy outcomes among maternal delivery discharges: stillbirth (ICD-9-CM codes V27.1, V27.3, V27.4, V27.6 and V27.7), preterm labor (ICD-9-CM code 644.2), multiple gestation (ICD-9-CM code 651) and known or suspected fetal anomaly affecting management of mother (ICD-9-CM code 655). Microsoft Access 2007 and Microsoft Excel 2007 were used to query discharge records and analyze data.[7]

Hospital and physician charges for care for infants conceived using ART/AI at Loma Linda University Medical Center (and other fertility centers) and delivered at this medical center were tabulated by hospital financial administrators and/or departmental financial accountants (for physician charges) for births occurring during 2012 and the first 6 months of 2013. Hospital and physician charges were adjusted for the charges of caring for a 'normal newborn infant', and a ratio calculated to compare similar charges for a late preterm or full-term infant delivered at our facility. The ratio of these two charges provides an estimate of the added cost burden for infants conceived by ART/AI, having a live birth and receiving neonatal care. Length of hospital stay for ART/AI-conceived infants was compared with that of a normal newborn at this center.

RESULTS

In 2009, births in California accounted for 12.8% of all U.S. resident births.[8] Women in California underwent 18 405 ART procedures in 2009, of which 15,953 embryos were transferred, resulting in 7155 pregnancies and 5710 live births, of which 30.1% were multiple births.[4] Embryo transfer procedures are summarized in Table 1, which documents the very low rates of elective single embryo transfer by maternal age in California and throughout the United States.[4]

Among ART/AI pregnancies there was a 4–5-fold increase in stillbirths identified from 2009 to 2011 compared with women whose pregnancy occurred naturally, whereas women with a history of infertility had a 2–3-fold increase in the rate of stillbirths (Table 2). ART/AI conceived pregnancies also experienced increased rates of cesarean section with associated complications and co-morbidities (41% on average), which were increased four-fold compared with those among naturally conceived pregnancies (10% on average); this rate was increased three-fold among women with a history of infertility but in whom there was a natural conception (30% on average). Mothers undergoing ART or AI had an almost fourfold increase in the rate of preterm labor compared with those with natural conceptions, whereas mothers with a history of infertility experienced preterm labor more than twice the rate of those with natural conceptions (Figure 1). Multiple gestations were increased 24–27-fold among women undergoing ART/AI compared with naturally conceived infants, whereas among those with a diagnosis of infertility this was increased ~10-fold (Figure 2). The mean maternal length of stay among women receiving ART or AI compared with those with naturally conceived infants was doubled as illustrated in Figure 3. A 2–3-fold increase in known or suspected fetal anomalies among ART or AI compared with naturally conceived infants was demonstrated, although among mothers with a previous diagnosis of infertility there was also an increase in known or suspected fetal anomalies (Figure 4).

Charges for maternal care during the perinatal period for years 2009–2011 are presented in Table 3. These costs do not include costs of ART/AI procedures or prenatal care, and are confined to costs incurred during the hospitalization in which delivery occurred. The significantly higher reported costs of perinatal care for ART/AI mothers reflect their frequent admission for preterm labor, prolonged hospitalization for antepartum testing, 'bed rest', medication to suppress preterm labor and the increased rate of

Table 1. Embryo transfer procedures[a] by maternal age, California and the United States, 2009

	Maternal age					
	< 35 years		*35–40 years*		*> 40 years*	
	California	*USA*	*California*	*USA*	*California*	*USA*
Number of embryo transfer procedures	3397	36 966	4822	35 620	2009	11 445
California as percent of United States	9.2		13.5		17.6	
Mean number of embryos transferred	2.2	2.1	2.7	2.5	3.2	3.0
Elective single embryo transfer rate	8.0%	7.4%	2.6%	2.8%	0.5%	0.5%

[a]Among patients who used fresh embryos from their own eggs.

Table 2. Stillbirth diagnoses among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011

Delivery discharges	*Year of discharge*		
	2009	*2010*	*2011*
ART/AI discharges	672	963	1255
ART/AI discharges with stillbirth diagnosis	19	29	26
Stillbirth diagnoses per 1000 discharges	**28.3**	**30.1**	**20.7**
Infertility discharges	539	497	611
Infertility discharges with stillbirth diagnosis	6	9	10
Stillbirth diagnoses per 1000 discharges	**11.1**	**18.1**	**16.4**
Natural conception discharges	509 235	491 533	483 469
Natural conception discharges with stillbirth diagnosis	2800	2715	2632
Stillbirth diagnoses per 1000 discharges	**5.5**	**5.5**	**5.4**

Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.
Bold values by year and by still births/1000 discharges associated with ART/AI, infertility, or natural conception illustrate the multi-fold increase in still births among ART/AI conceived pregnancies in California 2009–2011.

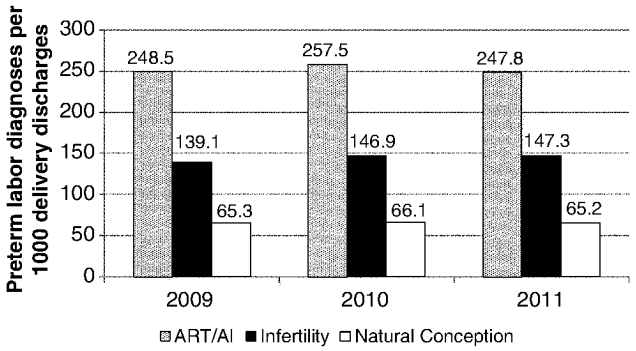

Figure 1. Preterm labor diagnoses among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011. Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.

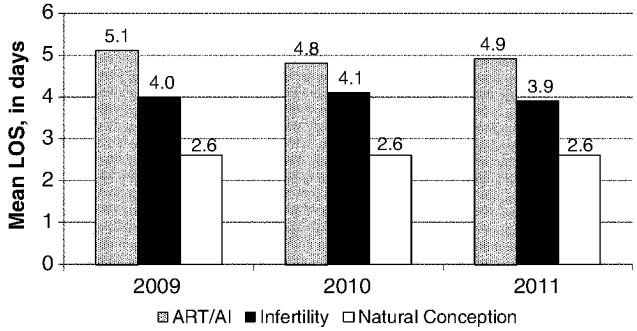

Figure 3. Mean length of stay (LOS) in days among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011. Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.

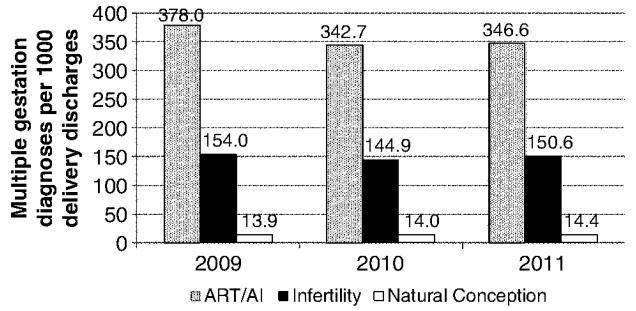

Figure 2. Multiple gestation diagnoses among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011. Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.

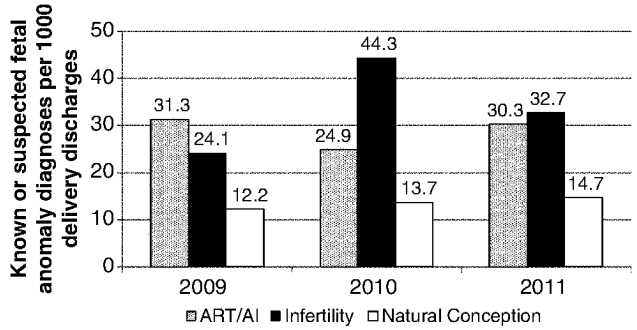

Figure 4. Known or suspected fetal anomaly diagnoses among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011. Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.

operative deliveries in these women. In California, ART contributed to an increase in multiple births that was higher than but not significantly different from those reported nationally.[4] Data from the CDC also show that California's rates of low birth weight and very low birth weight infants, as well as premature and very premature infants, exceed national averages.

Expected source of payment for ART/AI deliveries and deliveries among women with infertility occurring in California from 2009 to 2011 differed considerably from expected source of payment for naturally conceived deliveries. Although private insurance was the predominant source of payment for women receiving ART or AI (94%) and women with a history of infertility (95.6%), Medi-Cal (Medicaid) funding was the most frequent payer source for mothers whose infants were conceived naturally (48.2%); however, in this latter group a nearly equal number of women had private insurance or another third party payer (47.6%).

Hospital charges for the care of 82 infants (excluding 10 extremely premature infants who died on the first day) conceived using ART (79 infants)/AI (three infants) were substantially higher per infant than medical services for the 3465 naturally conceived who delivered as late preterm, early term, full term or post term as singleton infants (Table 4) provided care in our 'normal' newborn nursery over the same period. Hospital and physician services charges for infants born after ART/AI were significantly higher than

those charged for 'normal' newborn care. Charges for multiple births were per infant. Hospitalization in the NICU averaged 38.4 days (range 3–138 days) (95% CI 6–87) among ART/AI-conceived infants. There were 17 singletons (half of whom required NICU admission) 27 pairs of twins (with one stillborn, and four deaths shortly after birth) and six sets of triplets (in two sets of triplets death occurred soon after birth). Overall hospital reimbursement averaged 38%, whereas physician reimbursement averaged 32% for ART/AI infants.

DISCUSSION

Although the use of ART/AI has enabled many couples to have children, use of these technologies is associated with a substantial impact on perinatal outcomes in terms of stillborn infants, increased used of operative delivery, increased maternal length of hospital stay and maternal costs of care during the perinatal period.[9] In addition to the cost of achieving pregnancy, ART resulted in increased numbers of multiple, prematurely born and low birth weight infants, also contributing to increased health-care resources. Although some states have mandatory inclusion of ART and AI services in health insurance programs,[10] to date there has not been an estimate of either the total costs incurred or saved when insurance coverage has been made available. In European countries, where ART services are included under national health insurance schemes, the use of elective single embryo transfers is significantly increased, leading to fewer premature, low birth weight infants resulting from ART/AI pregnancies.[11]

Our data suggest that prior to inclusion of ART or AI services under state health programs, there must be implementation of existing professional guidelines[12] focused on elective single embryo transfer procedures. The goal must be to reduce the human toll in terms of stillborn infants, operative deliveries and low birth weight, premature infants born, so that offering these services becomes more widely available without unnecessarily burdening the limited resources of the health-care system.

Adashi *et al.* have stressed that 'our ultimate, if not immediate, goal is clearly a healthy singleton birth. Let us work together to ensure that the last disabled child has been born'.[13] Templeton has stressed that single embryo transfer is the only ethical approach for ART specialists.[14] However, as recently summarized by Kulkami *et al.*, the high incidence of multiple births in the United States remains as a consequence of fertility treatments in women of more advanced age. They estimated that 36% of twin births and 77% of triplet and higher order multiples were attributable to medically assisted conceptions. Among some providers there has been a decrease in the number of embryo transfer of three or more during *in vitro* fertilization (IVF) and a 33% decrease in the proportion or triplet and higher order multiple births attributable to IVF since the peak rates in 1998.[15] However, our data suggest that not all IVF providers in California have adhered to professional guidelines regarding the number of embryo transfers.

Reynolds *et al.* evaluated non-IVF fertility treatments from 1997 to 2000 and found ovarian induction and hyperstimulation as a leading cause of multiples births,[16] and Guzich *et al.*[17] evaluated women who underwent ovarian superovulation and intrauterine insemination and found a large proportion of pregnancies multiple births. It is clear that reducing the rate of multiple embryo transfer must be of the highest priorities. A clinical shift from ovarian hyperstimulation to elective single embryo transfer after IVF is likely to lower the still unacceptably high rate of multiple births with the associated risks of prematurity and low birth weight. Lambert and Mélançon[18] have elegantly argued that 'while couples may choose the level of risk that they are willing to assume when it is a matter of their own health; within the context of ART the future of the child must be considered vulnerable. Protection of the vulnerable is a matter of a physician's moral and ethical responsibility, and physicians are responsible for risk reduction or prevention when future generations are at stake'.

Using 2005 cost data from the Institute of Medicine, of the $26.2 billion spent on the costs surrounding the birth of a preterm infant, only $1.9 billion or 7% was associated with maternal delivery services.[19] Using cost estimates (from 2005) and ART birth rates from California in 2009, the costs for maternity care for ART pregnancies were $192 621 215 compared with $11 027 105 902 for naturally conceived infants (~2%). Information from the 2011 data set demonstrate an increase in this trend wherein costs for ART/AI maternity care were $35 767.50 per pregnancy versus $18 654 for a naturally conceived pregnancy, or a 1.9-fold increase in cost. Hospital and physician charges for the care of ART/AI-conceived infants are multifold greater than the care for a normal

Table 3. Total charges among ART/AI, infertility and natural conception delivery discharges, California, 2009–2011

Year of discharge	*ART/AI*		*Infertility*		*Natural conception*
	Median	*Ratio to natural conception*	*Median*	*Ratio to natural conception*	*Median*
2009	$30 557	1.91	$24 215	1.51	$16 017
2010	$34 515	1.99	$25 776	1.48	$17 379
2011	$35 768	1.92	$25 066	1.34	$18 654

Note: Total charges for patients discharged from Kaiser Permanente facilities are not represented here, as Kaiser Permanente does not submit total charges to OSHPD.
Source: California Office of Statewide Health Planning and Development, Patient Discharge Data, Public Files, 2009–2011.

Table 4. Neonatal characteristics and hospital and physician charges for 82 infants born after ART/AI.

	Birth weight (g)	*Gestational age (weeks)*	*Hospital stay (days)*	*Hospital charges ratio (× fold)*	*Physician charges ratio (× fold)*
	Mean ± 1 s.d. (Median)	*Mean ± 1 s.d. (Median)*	*Mean ± 1 s.d. (Median)*	*Mean ± 1 s.d. (Median)*	*Mean ± 1 s.d. (Median)*
Singletons	2866 (210) *(2749)*	36.0 (2.1) *(36.5)*	16.5 (4.5) *(12)*	48 (11) *(42)*	38 (9) *(31)*
Twins	2170 (355) *(1956)*	34.1 (4.1) *(34.8)*	27.5 (7.9) *(17)*	59 (29) *(47)*	62 (15) *(58)*
Triplets	1213 (298) *(1108)*	30.1 (2.3) *(30)*	83.5 (19.9) *(75)*	263 (89) *(229)*	187 (74) *(160)*

Source: NICU Admission Records, Office of Finance Loma Linda University Children's Hospital and Department of Pediatrics, Chief Financial Officer.
Medians are denoted in italics.

newborn. This increase is associated with the large percentage of multiple births, low birth weight and premature infants, several of whom had one or more birth defects (9%).[20] Medical costs for ART-conceived infants frequently switched from private or third party payer to state or federal funding after delivery (18.9%), which represents a substantial cost shift to public payers.

Additional costs for maternal care attributable to ART, as well as substantially higher hospital and physician charges for the care for infants delivered after ART/AI, are a growing medical economic concern for Californians and health policy-makers nationwide.[21] In an era stressing value in health care, it is incumbent on policy-makers to reduce these disproportionate costs by focusing on reducing prolonged antepartum hospital stays and the high number of cesarean sections associated with multiple gestations by encouraging single embryo transfer and developing incentives to do so. Elective single embryo transfer, when appropriate, would assist in reducing these costs by reducing maternal pregnancy and perinatal costs, and also reduce morbidities sustained by mothers because of the high rate of operative deliveries, as well as newborn care, as has been done in other countries.[22] There is precedence for this in Sweden and many other European countries.[23] Furthermore, costs of neonatal care would undoubtedly be substantially reduced if singleton infants were born primarily at term gestation.[24] The focus of ethical ART service providers should prioritize a pregnancy in which an infant is delivered at full-term gestation. It is doubtful that health insurance companies will be willing to include ART as a covered benefit if the expectation is deliberately skewed toward an outcome that is high risk and outside of professional guidelines. Although the cost of ART services has diminished in states with some form of mandate to include these services, the costs associated with pregnancy and infant outcomes await further analysis.[10]

Limitations of this retrospective analysis include reliance on non-federal hospital administrative data in a publicly available data set. The limitation of these data is due to lack of verification or audit of maternal discharge data by an independent auditor for completeness. Hospital charges or physician charges may not necessarily reflect costs outside of California. Furthermore, the ratio of charges to true cost may be different for hospital and physician charges and changes on an annual basis as a result of asymmetric fee schedule increases. The 2009 data regarding neonatal costs are based on 2005 data reported from the Institute of Medicine in 2007 based on national data and may under-represent current costs; extrapolation to 2013 costs would be expected to demonstrate similar proportions in disparate costs for infants born preterm. The ratio of costs for ART-conceived infants to naturally conceived infants reported for 2009 is probably unchanged; however, prematurity, low birth weight (including extremely low birth weight infants) and multiple births are significantly over-represented by infants conceived using ART.[24] We understand that charge data from a single large medical center including hospital and physician charges may not be representative of California as a whole, and is limited by small numbers; nonetheless, these charges are not dissimilar from those reported for all of California by Schmitt *et al.*[25]

In summary, the high proportion of multiple low birth weight infants who are too frequently prematurely born after ART could be substantially reduced if there was a focus on single embryo transfer that would meet a couple's desire to create a family as has been the focus in Sweden and many other European countries. Potential parents must more fully understand the consequences of multiple gestations (even twins) in increasing infant mortality, morbidities and longer term consequences of disabling conditions, including birth defects, which will require ongoing medical or rehabilitative interventions throughout childhood.[26–29] Incentives for physicians to continue multiple embryo transfer to achieve a higher rate of 'pregnancy success' within their clinic as reported to the Centers for Disease Control (if reported at all) must be replaced by a broader concern for the children of tomorrow that ideally should be born at full term and healthy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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