Double trouble: Should double embryo transfer be banned?

Running title: Should double embryo transfer be banned?

Dominic Wilkinson[1,2,3] , G. Owen Schaefer[1], Kelton Tremellen[4], Julian Savulescu[1]

Affiliations:

1. Oxford Uehiro Centre for Practical Ethics, Faculty of Philosophy, University of Oxford
2. Robinson Institute, Discipline of Obstetrics and Gynaecology, University of Adelaide
3. John Radcliffe Hospital, Oxford
4. Repromed, Adelaide, South Australia, Australia

Correspondence: Dr Dominic Wilkinson, Oxford Uehiro Centre for Practical Ethics, Suite 8, Littlegate House, St Ebbes St, Oxford, OX1 1PT, UK

Funding: This work was supported by a grant from the Wellcome trust, [086041/Z/08/Z]. DW was also supported for this work by an early career fellowship from the Australian National Health and Medical Research Council [1016641].

Acknowledgements:

We are grateful to Angeliki Kerasidou, Michael Dunn, Mark Sheehan and others at the Ethox centre for helpful comments on an earlier version of this paper

Abstract

What role should legislation or policy play in avoiding the complications of in-vitro fertilization? In this paper we focus on single versus double embryo transfer, and assess three arguments in favour of mandatory single embryo transfer: risks to the mother, risks to resultant children and costs to society. We highlight significant ethical concerns about each of these. Reproductive autonomy and non-paternalism are strong enough to outweigh the health concerns for the woman. Complications due to non-identity cast doubt on the extent to which children are harmed. Twinning may offer an overall benefit rather than burden to society. Finally, including the future health costs for children (not yet born) into reproductive policy is inconsistent with other decisions. We conclude that mandatory single embryo transfer is not justified and that a number of countries should reconsider their current embryo transfer policy.

Keywords

In vitro fertilization, multiple pregnancy, twin pregnancy, embryo transfer, ethics, clinical ethics

Word count

5756 words

Introduction

Since the birth of Louise Brown in 1978, more than 5 million babies worldwide have been born as a result of assisted reproductive technologies (ART) [1]. About 1.5 million in-vitro fertilization (IVF) treatment cycles are performed each year[2]. However, IVF continues to raise challenging ethical and legal questions. It remains at present an expensive treatment. It is associated with significant potential health-related complications, leading to concerted efforts to develop safer ways of providing treatment[3]. One important reason behind the increased health risk from pregnancy with IVF is the increased likelihood of multiple births[4]. Approximately 25% of successful cycles result in a multiple pregnancy compared with 1% of spontaneously conceived pregnancies[5]. The increased risk of multiple births from IVF is, in turn, often related to decisions to transfer multiple embryos instead of one embryo at a time (elective single embryo transfer, SET).[1]

In order to reduce the risk of multiple birth, a number of states have regulations or policies that limit the number of embryos that can be transferred at a time, particularly for younger women. For example, Hungary, Switzerland, India and Italy limit the number of embryos that can be transferred to 3, France and Japan generally limit to 2, while Sweden, Belgium, Turkey and Quebec require SET for most transfers [7, 8]. By contrast other countries, such as the US,[2] and UK,[3] do not

[1] Other forms of ART (for example controlled ovarian stimulation without IVF) are also associated with increased rates of multiple birth[6]. In this paper, we focus on issues relating to IVF, however, the central arguments potentially also apply to regulation of other forms of ART.

[2] The American Society for Reproductive Medicine has issued guidelines recommending restriction on the number of embryos transferred depending on the mother's age [9], but those recommendations do not have the force of law.

currently regulate the number of transfers, instead providing clinical recommendations for embryo transfer[7]. There are variations between countries in the nature of these regulations, in how rigidly they are applied, and in the wider context, such as the availability of public funding for ART and cryopreservation (freezing of eggs for future cycles).

What is the right approach to regulation of embryo transfer? Is it justified to restrict some or all women undergoing IVF to single embryo transfer?[4] We will focus in this paper on single versus double embryo transfer (DET) since it is this question that has led to most recent debate[12, 13], and there is more published empirical evidence about the risks of DET compared with SET than there is for transfer of larger numbers of embryos.[5] Later in the paper we will consider the implications of our arguments for multiple (>2) embryo transfer.

Background

In order to set the scene for the ethical arguments it will be useful to briefly review the usual process of in-vitro fertilization and embryo transfer. IVF involves a number of steps, including ovarian stimulation, collection of ova, fertilization, embryo

---

[3] HFEA regulations in the UK require clinics to set out policies that will reduce their multiple birth rate to 10%. [10] This has led some clinics to adopt policies that effectively mandate SET for younger women [11].

[4] We frame our discussion in terms of restriction of liberty (rather than, say, protection of interests) because this is the direct policy question being debated: whether double embryo transfers should be legally limited. (As noted below, the default in the past has been to allow transfer of greater number of embryos). While this emphasizes the issue of autonomy at the outset, we do not mean to dismiss other relevant issues relevant to policy such as prevention of harm. As we will argue, a central question is whether the harms (to woman, child or others) attributable to DET are sufficiently weighty that double embryo transfer should not be permitted.

[5] If DET should be banned (at least for some women), a fortiori, transfer of larger number of embryos should also be prohibited. However, if the arguments in favour of limiting DET do not succeed there is a further question about multiple (>2) embryo transfer.

culture, and embryo transfer[14]. At the start of a cycle of IVF the woman's ovaries are stimulated by the use of daily hormone injections. She is monitored by regular scans, and, at an appropriate level of maturity, the ova are retrieved via an ultrasound-guided transvaginal needle aspiration. Ova may be cultured with many sperm, or fertilized directly by intra-cytoplasmic sperm injection. It is usual for a number of embryos to be created and cultured for 3-5 days. At this point one or more embryos are transferred directly into the woman's uterus, while excess embryos are destroyed or frozen[14].

There are choices to be made at each of these stages. These can affect the numbers of viable eggs that are collected, the number and condition of embryos created, and, of course, the likelihood of a live-born child. Overall, only about 25-30% of IVF cycles result in a live-birth[14, 15]. One key choice relates to the numbers of embryos transferred. In the early years of IVF, practitioners would routinely transfer multiple embryos in an attempt to improve the chance of successful treatment[7]. Prior to the advent of modern cryopreservation techniques, multiple embryo transfer also avoided the need to dispose of excess embryos, as well as reducing the need for women to have repeated cycles of hormone treatment (with attendant medical risks). However, over time, with increasing recognition of the risks of multiple pregnancy, as well as improvements in IVF techniques, there has been a strong move to transfer fewer embryos.

There have been a number of studies comparing SET with DET. An individual patient data meta-analysis of 8 randomised trials and 1367 patients, published in 2010, found a 29% rate of multiple pregnancies following DET compared with only

2% following SET[16]. (The latter rate is equivalent to the spontaneous twin rate in natural pregnancies.) The live birth rate was also about 1.5 fold higher with DET (42% vs 27%). It is possible to overcome the lower live birth rate in SET by repeating cycles. Studies that have compared a repeated SET strategy (where unsuccessful single embryo transfer is followed by another cycle using a frozen embryo) with DET have found very similar rates of at least one live birth (38% vs 42%), with only very low rates of multiple birth (~1%)[16]. On the other hand, DET results in a larger overall number of live-born children. In one trial, with 660 women randomised to either DET or repeat SET, there were 60 additional live-born children in the DET group[17]. Maternal age has an important impact on these statistics; older women (≥40 years) have lower rates of live birth with either SET or DET, and lower rates of multiple pregnancy [18].[6]

What is the impact of DET on outcome for the child? Children born following DET in the previous randomized trials were at a higher risk of being born preterm (40% vs 13%), and of having a low birthweight (24% vs 8%)[16]. Six percent of pregnancies following DET resulted in very preterm delivery (before 32 weeks gestation) compared with <1% of pregnancies following SET[16]. Perinatal mortality (stillbirth or neonatal death) was higher in an Australian population study (19.1 per 1000 live births with DET vs 13.2 per 1000 live births with SET) [19]. Complications requiring neonatal care were more common following DET (34% vs 18% in one trial) [17]. Long-term complications are relatively rare, and the evidence is mixed. They are not necessarily apparent in randomized trials. A Danish study found no

[6] For this reason, even countries with policies that limit DET may permit it in older women.

significant increase in neurological disability in IVF twins compared with IVF singletons[20].[7] The rate of cerebral palsy was 3.2 per 1000 for IVF twins, compared with 2.5 per 1000 for IVF singletons.[8]

DET is thought to increase the risk of a number of maternal complications of pregnancy, though this has not always been clearly shown in randomized trials[24]. One study found a considerably higher risk of premature prelabour rupture of the membranes (8.5% vs 0.8%), and almost double the risk of severe bleeding before or after birth (28% vs 16%)[17]. In another Swedish population study, mothers had significantly higher rates of pre-eclampsia and cesarean section following DET compared with two IVF singleton pregnancies[25].

These increased risks with DET translate into increased societal and health care costs (including short and long-term care) for both mother and child[26, 17, 27]. A recent UK study, modeling costs over a 20 year period, found that DET cost an additional £2200 (US$3625) per cycle, and £27,000 (US$44,487) per live birth. However, the difference in cost is affected by the age of the woman, and by the availability of frozen cycles[27]. In older women (above the age of 36), DET may be cost-effective in terms of total health service expense and maternal quality-adjusted life years compared with SET[26, 27].

---

[7] Although in the general population twins have higher cerebral palsy rates, IVF twins may be less affected. Identical twins who share a placenta or amniotic sac have a substantially higher rate of complications (and neurological morbidity) [21]. However, twins arising from DET are dizygotic (non-identical) and consequently have fewer complications.

[8] One way of reducing complications from multiple pregnancies associated with IVF has been to employ multifetal pregnancy reduction, with selective termination performed to reduce pregnancies to singletons or twins. However, complication rates in reduced pregnancies remain higher than non-reduced pregnancies (of the same number). [22] There are potential neurological complications in the remaining fetus/fetuses.[23]

Table 1 summarises the incremental risk or benefit of DET. With these in mind we will now appraise the three principal arguments in favour of mandatory single embryo transfer.

	Estimated absolute risk difference
Multiple pregnancy	+27% [16]
Live birth	+15% (+4%)* [16]
Preterm delivery	+27% [16]
Low birth weight (<2.5kg at birth)	+16% [16]
Neonatal death	+0.3% [19]
Caesarean section	+34% # [25]
Severe bleeding (for the mother)	+14% [17]
Pre-eclampsia	+7% # [25]
Health Service costs (per cycle)	+ US$3625 [27]

Table 1: Estimated risks/benefits and costs of Double Embryo Transfer compared with Single Embryo Transfer[16, 19, 25, 17, 27]. These estimates are derived, where possible, from recently published meta-analyses or large population based cohort studies. We acknowledge that there are differences between studies in the rates of these morbidities, and that some of these rates and costs may be disputed. The rates here are designed to provide a context for ethical discussion, rather than a definitive estimate.

*benefit compared to repeat SET

#risk for mother of IVF twin pregnancy (following DET) compared with two IVF singleton pregnancies

SET: (elective) Single Embryo Transfer. Following fertilization a single fresh embryo is transferred into the woman's uterus.

Repeat SET: Repeated Single Embryo Transfer. Additional cycles of IVF are performed after SET with thawed embryos. This may occur because of unsuccessful first cycles in order to achieve a single live birth (RepeatSET^{1}), or in order to achieve at least two live births (RepeatSET^{2}) e.g. because of a desire for more than one child.

DET: Double Embryo Transfer. Following fertilization two fresh embryos are transferred into the woman's uterus.

subDET: Substituted Double Embryo Transfer. If DET is chosen over SET, a different pair of embryos are transferred (that would not otherwise have been transferred)

ITDET: Identical Twin Double Embryo Transfer. If DET is chosen over SET, a single early embryo is divided into two embryos that are then transferred.

Box: Actual and Theoretical Embryo Transfer policies

1. Risk for women?

As already noted, one reason to prefer SET is because of the lower rate of complications for women: less bleeding, less premature delivery, fewer caesarean sections. Furthermore, if a policy of repeat SET is adopted, there is only a marginally higher live birth rate with DET. Prima facie, if two treatments are equally efficacious, but one treatment has a higher complication rate, it seems legitimate to prefer the less risky alternative.

However, policy or law that mandate single embryo transfer cannot be based simply on the interests of women. This is for at least two reasons. First, we can rely on a keen observation from Mill in *On Liberty*: individuals are in the best place to determine whether some state of affairs is in their interests[28 ch. 4]. Other members of society, policy makers or physicians may have views about whether particular costs are worth the benefits, but none of them will have direct insight into the interests of the individuals seeking out IVF. A policy of refusing DET because it is not in women's best interests would be clearly paternalistic.

Some women clearly favour DET[18]. A multi-disciplinary project, found that many women viewed the risks of multiple pregnancy as being strongly outweighed by the risk of not having a baby[29]. A significant proportion of women seeking IVF would prefer a twin pregnancy to a singleton[30, 31]. This preference can arise because it involves potentially fewer IVF cycles (and consequently lower personal financial cost), a desire to minimize the chance of the perceived worst outcome (no child), or a desire to have more than one child[30]. In the mid 2000s the average cost of a standard IVF cycle was US$12500 in the United States, $8500 in Canada and

$6534 in the United Kingdom. [32] Repeated SET may also have additional psychological burden of failed cycles[29]. While it appears that the chance of live birth is similar with repeat SET and DET, the chance of no live birth (despite repeated cycles) is not equivalent. Dropout rates are high in IVF treatment [33]. Most women will only be able to undertake a limited number of cycles, because of the cost, public funding restrictions, or because of falling fertility with time. In one large trial, the cumulative rate of no live birth (i.e., the proportion of women who did not achieve at least one live birth after repeated embryo transfer with frozen embryos if desired) was 56% in the SET group and 49% in the DET group [34].

Second, there is special reason to refrain from interfering with people's choice over what they do with their bodies. Mill makes the point that: "Over himself, over his own body and mind, the individual is sovereign" [28 p. 26]. Similarly, Dworkin describes a "prophylactic line that comes close to making the body inviolate" [35 /p. 39]. This is typically used to indicate a special prerogative over what is done to one's body.

The principle of personal autonomy and the inviolability of the body is usually construed as a negative right, a right to refuse or resist external interventions. It does not necessarily give an individual a positive right to demand medical treatment[36, 37]. However, there are two special features of embryo transfer that would suggest that patients should be able to choose how many embryos are transferred. Firstly, this is not the case of postulating a positive right to receive certain treatments. A woman requesting DET is not requesting a drug or a procedure or a treatment that she would otherwise not receive. She is already going to receive IVF and embryo

transfer. Rather, the choice of numbers of embryos transferred is, like the right to bodily integrity, akin to a negative right. At issue is whether, *given that a procedure will occur*, it will involve one method (SET) or another (DET). Whether one or two embryos are transferred involves a trivial difference in the physical procedure involved.[9] To restrict the procedure, contingent on it occurring, to SET is to limit the woman's options concerning what may be done with her body. As in the case of other questions of reproductive liberty, the ethics will crucially turn on whether considerations like the interests of children can plausibly override the right against interference.[10]

Secondly, we might think that a woman has a special moral claim over what happens to her embryos that is importantly different to her relationship to other medical treatments. There is a sense in which an embryo is the flesh and blood of the couple seeking IVF, at least in the majority of cases where donor embryos are not being used. Unlike a drug or surgical implement, the embryo and couple share a biological relation that is frequently taken to incur certain rights (as well as responsibilities). And even in the case of a donor embryo and no biological relation, there is an 'adoptive' relationship not unlike the adoption of a child – which, again, leads to rights and responsibilities. The content of those rights might be understood as a sort of property-right. There is great division over whether there is property in the body or in human tissue[38-40]. If there is such a property right, the embryo is

[9] A speculum will be inserted into the woman's vagina, and a catheter passed through the cervix. The only difference between SET and DET is whether one or two 0.1mm embryos are inserted into the uterus.

[10] We do not mean to suggest that this right is absolute. It is, rather, a pro tanto right – one that has significant strength, but can be overridden under certain circumstances. The next sections will discuss whether such circumstances obtain in the case of DET.

plausibly the property of the couple at least until it becomes a person. This would explain why women have the right to destroy the embryo or fetus prior to the development of moral status. Restricting women's ability to transfer multiple embryos would amount to a severe infringement on her property rights.[11] However, even if embryos are not considered to be property, we usually think that women and couples have a special legal and ethical right to make decisions about the fate of their embryos.[12] Although this right is not absolute, it does translate to a right to decide whether spare embryos are donated, used for research or destroyed. This can most sensibly be understood as particular instantiations of a more general right: the right to determine what is to be done with the embryos (subject to resource constraints). This general right appears to capture the relevant similarity between the particular rights that are given – a right to control the embryos, whether based on strict property concerns or more general relational considerations. But one thing that can be done with embryos is to transfer multiple at a time. The general conferral of dispositional rights over couples then implies a (pro tanto) right to determine how many embryos should be transferred.

The principle of autonomy underpins the concept of informed consent for medical procedures. Clearly, it is vital for women undergoing IVF to be aware of the relevant risks and benefits for themselves as well as the potential harms to

---

[11] There may be some cases of justified paternalistic restriction on inserting property into one's body, as in the case of self-mutilation or severe self-harm (such as swallowing a sharp object one owns). But those exceptions arise only when the action involves highly likely and very substantial harm; the relative risks of multiple pregnancy, while non-negligible, hardly rise to that level.

[12] US courts have sometimes regarded stored embryos as having a status intermediate between property and persons. More recent decisions typically have granted couples disposition over their embryos equivalent to that given to transferrable property, subject to contract law [41].

others[42]. One obvious and uncontroversial policy would be to adequately educate and inform women about these risks and benefits. Such education programs increase the acceptability of SET to women, and reduce the number of women desiring twins[43]. However, where patients are fully informed, restrictions on treatment cannot be based on the risks to the individual themselves. After all, we allow women to choose elective caesarean section, with increases in risks of haemorrhage, hysterectomy and cardiac arrest[44].[13]

Restrictions to individual liberty can generally be justified only if there are harms to third parties [28 p. 26]. We acknowledge that the numbers of embryos transferred might cause harm to others. The key question, then, is whether the third party harms from DET are weighty enough to justify overriding the woman's autonomy.

2. Risks to the child?

Twin pregnancy appears to confer a number of increased risks on children, particularly of early delivery, need for neonatal care, neonatal death and (possibly) long term developmental problems. Concern for the children conceived by IVF might well be thought to provide the strongest rationale for mandating SET. Stillman, writing recently in defense of SET, noted "The potential children, those at greatest risk of the complications associated with multiple pregnancy, are unable to advocate

[13] There is an interesting contrast between Sweden's attitude to SET (mandatory unless exceptional circumstances) [7] and caesarean section on demand (discouraged but permitted) [45].

for themselves. It is the professional and ethical responsibility of the physician-led clinical team… to advocate on their behalf." [42]

However, concern for children's welfare does not automatically mean that governments or physicians are justified in overruling parents' decisions[46]. There are a range of risks that we permit parents to make. For example, we allow parents to drive their children in a car (with approximately a 1 in 1000 risk of death over childhood), involve them in contact sport, or to decide not to vaccinate[47, 48]. We give parents considerable latitude in the rearing of children, even when different life-choices lead to predictably worse health outcomes, so long as their choices do not rise to the level of abuse. And we would not normally think that choosing to have twins is abusive, any more than it is abusive to choose (say) to live in a neighborhood with higher rates of violent crime and worse healthcare services. The question is whether the risks from DET constitute a "substantial risk of serious harm"[46].

Next, the risks of different embryo transfer policies are different from risks involved in other decisions that we make. They represent a special case because, potentially, one of the children *will not otherwise exist*. Suppose there are two embryos available, A and B, and a couple is trying to decide whether to transfer just A (SET), or A and B (DET). If the couple decides to transfer A and B, both resultant children are exposed to the health risks of multiple birth. Child A_2[14] might have a complaint in the future against her parents that she was exposed to unreasonable

[14] The subscript notation A_2 here indicates a child born as part of a twin gestation.

significant harm - had the couple decided to merely transfer embryo A, the resultant child A_1[15] would have had a lower risk of being premature etc. However, child B_2 has no such complaint. If the couple had decided to undergo only SET, child B_1 would never have existed. While there may be some cases where one's life is so bad it is better never to have lived at all, almost all actual cases like child B_2's will be worth living. We should note that the conditions described above would sometimes not be the case – for example, if a couple desired two children, and used SET to transfer both A and B in separate cycles. In such a case, both A_2 and B_2 could claim to have been harmed from the risk of being transferred together. In practise, because of the personal and financial cost involved, many couples who have had a successful SET IVF cycle would not go on to have additional children using ART.

This is an instance of a more general philosophical issue, the non-identity problem[49 ch. 16]. The non-identity problem occurs when decisions will affect the wellbeing of future people, but also affect the identity of those people. In such cases it often seems intuitively correct to say that someone was harmed (for example child B_2 in the above case), but this is undermined by the fact that the individual would not have existed but for that decision. Sometimes, conceding that no one was harmed is deeply counterintuitive (for example, for a devastating environmental policy that changes the identity of future generations). The SET/DET case might not appear so puzzling – perhaps we can just concede that child B was not harmed, and focus our

[15] A_1 indicates a child born as part of a singleton pregnancy

attention on the weighing up of competing considerations for child A_2 and the parents.[16]

However, having recognized the significance of the non-identity problem, there is a theoretical solution available that would eradicate the harms of multiple births in at least some SET/DET cases, a policy of substituted DET (subDET) (Box). SubDET would be an option for any IVF cycle with at least 3 viable embryos, A, B and C. If the woman seeking IVF opts for SET, we would transfer embryo A.[17] If she opts for DET, we would transfer embryos B and C instead. That way, even though resultant children B_2 and C_2 would be exposed to risks stemming from multiple birth, neither have been harmed. If the parents had opted for SET, B_1 and C_1 would never have existed.

SubDET may not be a practical option, since many IVF cycles do not generate 3 viable embryos of equivalent apparent quality. IVF doctors typically select embryos based on their morphological characteristics [50]. In our experience it is not common for there to be three high quality embryos available. Consequently, subDET may involve selection of two apparently lower quality embryos (B+C), with a lower chance of successful pregnancy. If this were the case it may lead women to choose SET

---

[16] In some circumstances, the non—identity problem might mean that neither A_2 nor B_2 are harmed. If multiple embryo transfer were to lead to a sufficiently severe neurological disability in A2, it might be thought to be identity-changing, such that the disabled child A_2 is different from the non-disabled singleton A_1 who might have existed. As noted, the harms attributable to DET are not likely to be of this severity. One unique feature of the harm in DET is that, in almost all circumstances, neither twin will ever be in a position to complain about being harmed from being a twin – since they will never know whether they were embryo A (destined to exist in both cases) or embryo B. At best they would know that they had a 50% chance of having been harmed from being transferred as a twin.

[17] If further SET cycles were undertaken after a successful pregnancy, embryos other than B and C would be used in order to maintain non-identity.

over subDET, even if subDET would avoid possible harms to resultant children. However, there is a further theoretical solution available in situations where there are not spare embryos of adequate quality – Identical Twin Double Embryo Transfer (ITDET). Artificial embryo twinning could be used to divide embryo A at the 6-8 cell stage [51]. The resultant identical twin embryos, if successfully transferred and gestated, would result in children A'_2 and A''_2. Although genetically identical with A_1, neither A'_2 nor A''_2 could claim to have been harmed since neither would have existed without the embryo twinning procedure.[18]

While some might find this to be a compelling philosophical solution, it has a whiff of sophistry. SubDET or ITDET will not affect the negative outcomes that accrue to children in multiple births. All it does is potentially increase the cost of IVF (more embryos may need to be produced) while ensuring that no children are worse off than they would otherwise have been (i.e. there are no person-affecting harms). It would be hard for many people to believe that subDET or ITDET is really an improvement over DET. To avoid this implication, the opponent of DET could turn to another way to resolve the non-identity problem – by appealing to non-person-affecting or 'impersonal' harms. Impersonal harms in this context refer to harms based on an effect on the well-being of individuals who exist no matter their identity. The idea is that some choices are harmful impersonally because they lead to people

[18] ITDET has not (to our knowledge) been performed in humans, and it is unknown whether it would be associated with harms to the children thus conceived. Such harms would need to be taken into account were ITDET to be explored as a way to address possible harms of DET. (Artificial twinning has been used successfully in several other species[51]).

living lives that are not as good, even though no individual is worse off[49 ch. 16].[19] Substituted DET would mean that at least one resultant child per successful IVF treatment will live a life with a higher chance of illness or impairment (and thereby lowered expected well-being) than the child who would exist if SET had been chosen instead.

If we accept the existence of impersonal harms, it is important to determine their weight relative to person-affecting harms. If impersonal harms are just as important as person-affecting harms, subDET is no improvement over DET (this is sometimes referred to as the 'No Difference' view) [49 ch. 16].(Appendix Tables) It is just as bad to harm child A_2 as it is to bring child B_2 into existence in a harmed state. However, if we accept this view about impersonal harms it may have significant implications for other reproductive decisions (for example, it may imply that there is a strong moral imperative for parents to choose an embryo with the best possible life) [52]. Moreover, it would seem to imply that it is just as bad for a parent to refuse cochlear implants for their congenitally deaf child (or to deliberately deafen them) as it would be to select a deaf embryo[53, 54]. This seems implausible. An alternative view is that impersonal harms, though significant, generally have less force than person-affecting harms[55-57]. Perhaps only a large number or magnitude of impersonal harms are equivalent to the same person-affecting harm. If that is the case, it becomes a question of how we should weigh up the person-affecting benefit for the mother of subDET against the impersonal harm of multiple gestation.

---

[19] In the environmental damage case, future people live much worse lives than the (different) people who would have lived had the environment not been damaged. This seems impersonally bad.

Finally, if our embryo transfer policy is to take into account impersonal harms (reductions in wellbeing that do not make anyone worse than they would otherwise have been), it seems ad hoc not to also consider impersonal (existential) *benefits*. Different embryo transfer policies are ultimately what are sometimes referred to as "different number" cases[49 ch. 16]. The difference between SET and DET is not merely the difference in risks for child A, but also that we are bringing one individual vs. two into existence. At the core of this is the question of whether someone can be benefitted by being brought into existence. If one thinks it is a benefit, then we would have to weigh the small harm to the first child against the (perhaps large) benefit to the second child of existing at all.[20] After all, we might imagine that B_2 is grateful to be alive, and for her parents' decision to use DET rather than SET. As noted earlier, providing DET to 330 Swedish women led to 60 additional children being born [17]. The impersonal harm to child B_2 from twin gestation (with a small additional risk of prematurity and being small birth weight, and a 3 in 1000 risk of death) seems much smaller than the impersonal benefit of a live worth living for B_2 and C_2.

To summarise, focussing on person-affecting harms favours SET, but this could be avoided by substituted DET. The No-difference view would favour SET over subDET, yet it has other significant implications for reproductive decision-making that are potentially troublesome. If impersonal benefits are to be considered, DET may be favoured, depending on how harms to children are balanced against potential

[20] Such views are often taken to lead to a counter-intuitive or 'repugnant' conclusion that it is generally better to be bring more and more people into existence, even if each additional person only has a life barely worth living. However, this population ethic need not be endorsed here: we can merely make the negative claim that such a benefit means one should not interfere with reproductive choices, without endorsing the positive claim that such a benefit implies it is better to maximize reproduction.

benefits to other children. Interestingly, a policy of repeat SET^2 (where enough cycles of SET are funded or permitted to ensure that at least as many children are born with SET as would be the case with DET) is pareto optimal (from the point of view of children conceived) on all of the philosophical views that we have considered (Appendix table). This would count in favour of repeat SET^2, though does not necessarily mean that this should be the only option available to women.[21]

We do not propose to settle here the seemingly intractable philosophical questions in population ethics about whether the benefits and harms of bringing someone into existence count equally or at all, or whether impersonal and person-affecting harms are equivalent. Nor are we proposing that subDET or ITDET should be made available. Our aim is more modest. We have highlighted that concerns about harms to children with different embryo transfer policies depend upon contested philosophical assumptions. Issues surrounding embryo identities have not been adequately addressed in the literature and by policymakers. The non-identity problem makes harms and benefits to resultant children uncertain. In contrast, earlier concerns over the rights and interests of women undergoing IVF (whose identity is not in question) remain much more certain. We contend that the relative certainty of the rights-violations should make them weigh heavier in policy considerations, militating against restrictions on DET.

[21] As noted earlier, the additional physical, financial and psychological burden of additional IVF treatment cycles leads at least some women to prefer DET over repeat SET.

3. Costs to Society?

The preceding discussion has focused on the interests of women and children born by IVF. But these are not the only parties affected by the decision to undergo SET vs. DET. There are significant costs borne by hospitals, the state and society at large that may need to be taken into account. If complications arise from multiple births, this will require greater medical care and resources. One estimate, based on the number of IVF twins in the United States, put the total annual additional cost related to multiple embryo transfer at almost $1billion[58]. Spending those resources will either require the population at large to face increased costs (through increased taxes for public insurance programs, or increased insurance premiums for private programs), or for resources to be diverted from other patients.

By focusing on the costs to society we could avoid the challenging issues of non-identity outlined in the previous section. However, there are several factors that undermine the argument from excess cost as a justification for mandatory SET.

The first of these is that analyses of the costs of DET typically focus only on the financial costs of treatment, while ignoring the potential benefits. We noted in the previous section, that DET also results in the live birth of extra individuals (approximately an extra 5 children for every 10 live born children from SET). Re-analysis of the costs per child born (and including all of the excess health costs) favours DET, costing approximately US$3790 less per live born child compared with

SET.[22] However, figures based on economic modeling of projected lifetime tax earnings (subtracting lifetime direct government costs eg education, health, pensions) are even more striking. Such modelling suggests that there is a net economic benefit of £110,000, or US$155,000 for each child conceived by IVF[59, 60]. Based on the same estimates of total numbers of twins conceived by IVF in the United States[58], the total economic benefit of multiple births from IVF in the US is US1.8billion annually, yielding a net benefit of US$800 million per year.

There are several possible counter arguments that might be raised here. First, cost effectiveness analysis is usually confined to health benefits and risk. Why should we count future tax income in assessment of IVF policies, but not in other areas of health? One reason might be that IVF is a special case because it involves the addition of extra individuals to a society. We should therefore think broadly about the costs *and benefits* of IVF for public finances in a way that we do not for other medical treatments. Second, it might be noted that an argument drawing on the long-term fiscal benefit of healthy members of society would also count in favour of more liberal funding of in-vitro fertilization, or more generally, in favour of reproduction. It may not be the case, though, in parts of the world with significant overpopulation or with different levels of taxation and public expenditure. The problems of global overpopulation would potentially count against policies that significantly added to the population. However, we would note that our aim here was not to mount a case in favour of fecundity. Rather, we have pointed out that the economic argument against

[22] Using figures from Scotland et al [27], in young women – cost per live-born child with DET is 22341.7, compared with 24647.6 (calculated from Scotland et al table 1 – 60 children per 100 cycles DET, 45 children per 100 cycles repeated SET1)

DET in developed countries is flawed. Finally, although the problems of global overpopulation might legitimately affect reproductive policy, we contend that it would be unfair to impose restrictions on reproduction for those who require medical assistance to reproduce when there are no restrictions on those who reproduce naturally.[23]

Next, the additional costs of DET are largely related to excess future health costs for the child. For example, 80% of the additional health costs related to paediatric health costs in one trial[17]. Yet, future health care costs for a child are not usually taken to be sufficient justification for interfering with reproductive decision-making. For example, the estimated lifetime medical costs of a child with cystic fibrosis(CF) are more than US$160,000 [61]. These costs strongly favour the use of pre-implantation genetic diagnosis for couples who are carriers for CF rather than natural conception and termination of affected pregnancies (by a net US$182,000).[24] They would clearly favour prenatal diagnosis and termination of pregnancy over live-

[23] There are differences between natural reproduction and artificial reproduction that make it easier for governments to limit artificial reproduction than the natural form. Further, limits to natural reproduction might be thought to threaten rights (for example to privacy) that are not at stake, or less at stake when discussing numbers of embryos transferred. However, as we argued earlier, women's negative right against state interference in reproductive decision-making, includes whether to undergo DET. Infertile women are already at a disadvantage (struggling with infertility) and may be spending significant resources to alleviate it. Restricting their reproductive rights only serves to disadvantage them further. Furthermore, countries like Sweden and Turkey not only do not restrict natural reproduction, they have adopted a range of policies to positively promote childbirth.{Gauthier, 2007 #2463}{, 2013 #2462} It would appear hypocritical to restrict access to DET on the basis of concerns about overpopulation, while at the same time to be positively promoting reproduction by other means. Finally, population growth attributable to artificial reproduction constitutes only a tiny proportion of global population increase. The world population has increased by approximately 3 billion since 1978, while as noted there have been 5 million births from IVF (approximately 0.17% of global population growth). Restrictions on IVF are likely, therefore, to be highly inefficient means of curbing population growth.

[24] This estimate incorporates future earnings and tax. However, even if this is ignored and only health costs are assessed, given the approximate cost of $17000 for one cycle of PGD, it would appear to be clearly cost effective to perform PGD or prenatal diagnosis over live birth.

birth of an affected child. However, we would usually think it completely inappropriate to require carrier couples (through policy or law) to undergo IVF rather than termination, or termination rather than continuation of a pregnancy. Even in the case where a couple were already undergoing IVF, the state would not require a couple to undergo pre-implantation genetic diagnosis (PGD), and transfer of a non-affected embryo.[25] In the case of cystic fibrosis, reproductive autonomy outweighs the considerable future health care costs to the child. Why, then, should the much smaller incremental costs of DET (~US$3600) outweigh women's freedom to make reproductive decisions that are important to them?

Third, focussing purely on the costs (or incremental costs) of DET over SET, may ignore some of the downstream effects of a policy that mandates SET. Restricting access to IVF, for example by declining to publicly fund DET, may force women into the private system. In countries without a private health system, women may decide to travel overseas for treatment, and access to transfer of larger numbers of embryos [62]. There is clear evidence from the US and elsewhere that funding arrangements for IVF impact upon the numbers of embryos transferred[63]. Higher levels of financial support for IVF (for example through mandated insurance coverage, or through public health systems) lead to lower numbers of embryos transferred and lower multiple birth rates[64, 65]. In the United States, one IVF cycle costs approximately 44% of patients' annual disposable income[32]. It is unsurprising

[25] Most parents in this situation would be likely to choose pre-implantation genetic diagnosis, however, it is possible that some parents (for example with a strong religious objection to disposal of viable embryos) would choose to avoid PGD.

that women who are forced to pay such a high financial cost for infertility treatment choose multiple embryo transfer, with a higher chance of live birth.

Finally, even if the excess costs of DET were to justify policy that limited access to DET, there would be fairer ways of doing this than simply mandating SET. One option would be to address the financial disincentive for women to use SET. At least one US insurer has opted to cover women who choose SET for the costs of cryopreservation and an additional cycle if the first is unsuccessful[42]. Another IVF clinic offers a 'shared risk' program, with a fixed cost for a series of SET treatment cycles[63]. For public systems or insurers that only currently fund SET, one alternative would be to allow women to pay the incremental cost of DET[26] (rather than the full cost of IVF). After all, if the reason not to fund DET is because of concern about excess cost, there would be no reason not to allow treatment if women were prepared to pay the additional cost associated with DET.

Multiple Embryo Transfer

One objection to the above arguments would point to some of the very serious complications of higher order multiple pregnancies. Although our paper has focused on the question of DET versus SET, some of the same arguments would extend to three or four embryo transfers. A Sorites-type argument might be run against any limits on numbers of embryos transferred. Why stop at two embryo transfer, why not three, why not eight[66]?

[26] As noted, DET is potentially cheaper than SET in the long-run. However, if only health-related costs are to be included, patients might be required to pay $3600 for a DET rather than SET cycle. This is approximately half the full cost of an IVF treatment cycle in the UK [32].

We accept that some of the arguments that we have covered could also work against limits on higher numbers of embryos transferred. However, we suggest that the argument in favour of transfer of higher numbers of embryos is weaker for several reasons. A much smaller number of women seeking IVF treatment desire higher order multiple pregnancy (i.e., more than twins). In one US study, 20% of women preferred a multiple over a singleton birth. Of these, 94% preferred twins, while only 6% preferred more than this[43]. Furthermore, and perhaps most importantly, there appears to be no improvement in the live-birth rate with transfer of three or more embryos compared with DET, while there is a higher rate of adverse outcomes[18] [67]. There is therefore little positive reason in favour of three (or greater) embryo transfer, while the costs would be significantly greater.[27]

Conclusions

In this paper we have outlined a series of concerns with policy or legislation that would mandate single embryo transfer for all or some women seeking IVF treatment. We identified flaws in each of the three major arguments in favour of SET. DET is associated with increased risk for women, but twin pregnancy is strongly desired by at least some women needing IVF. Additionally, DET reduces the chance of no-live birth despite repeated cycles, and reduces the personal and financial costs for some women. DET is clearly associated with increased rates of preterm birth and

[27] Only 1% of three or four embryo transfer cycles performed in the UK between 2003-7 resulted in live-birth of three babies. This compares with approximately 7% of two-embryo transfer cycles resulting in twin-live-birth [18] Correspondingly, the economic benefit from additional tax-paying members of society is likely to be small. In the same study, the adjusted odds ratio of live birth with DET compared with SET was 1.65 (confidence interval 1.54-1.77), while the odds ratio of live birth with three embryo transfer (compared with SET) was 1.62. [18]

need for neonatal care. Yet, these increases are modest compared with other health risks and concerns about risks for the child are made more complex by the non-identity problem. When two children are born following DET, at least one of the children has not been harmed (because they would otherwise not exist). DET results in more living children, highlighting the possibility of benefit as well as harm from multiple gestation. Finally, DET is associated with increased costs, yet if the lifetime benefits to public finances are taken into account, DET provides a net benefit. Furthermore, the costs of future health care for a child are not usually taken to be sufficient grounds for limiting women's reproductive decisions.

The preceding discussion is meant to put serious pressure on policies restricting or prohibiting DET. Countries or states that currently mandate SET such as Sweden and Quebec should review and potentially repeal their policies. However, this does not mean that concerned physicians and policymakers should do nothing in reaction to evidence that DET leads to additional health complications. At the very least, pure persuasion is still an option. Physicians can present the risks and burdens of DET (along with the benefits), engaging the couple or woman in argument about what they believe is the best course, in the hope that the patient will adjust their behavior accordingly[68, 69]. Similarly, policymakers can develop educational campaigns to raise awareness of the risks and benefits of SET vs. DET. This has the advantage of leaving the decision in the hands of the individuals undergoing IVF, both respecting their autonomy and ensuring that their own values will be determinative of the ultimate decision. Indeed, it may improve patients' own decision-making.

Whether or not the above arguments succeed in convincing those who are strong advocates of SET, we have identified several important issues that are often overlooked in the debate over whether and how to regulate IVF. Policymakers, administrators and physicians should carefully consider these factors when deliberating over which policy to endorse, just as patients need to carefully consider all the factors involved when deciding between SET and DET. We have also demonstrated that different philosophical views (often taken to have merely theoretical interest) might yield strikingly different answers for this very practical question of how many embryos should be transferred.

Appendix

	Children existing	Person-affecting harm (compared with SET)[X]	Impersonal harm (compared with SET)[Y]	Impersonal (existential) benefit (compared with SET)[Z]
SET	A_1 (or B_1)*	-	-	-
Repeat SET[2]	A_1 and B_1	0	0	B_1
DET	A_2 and/or B_2*	A_1-A_2	A_1-A_2	B_2
SubDET	B_2 and/or C_2	0	A_1-B_2	C_2
ITDET	A'_2 and/or A''_2	0	A_1-A'_2	A''_2

Appendix Table 1: Harms and benefits of embryo transfer policies

The nomenclature A_1 here indicates a child born following a singleton pregnancy, while A_2 indicates a child born following a twin pregnancy.

*Since SET policies often involve the possibility of repeat cycles with frozen embryos, choosing SET will in some instances result in the live birth of child A, and in others, the live birth of child B. From McLernon et al [16], choosing SET will result in a 27% probability of live birth of child A, and an 11% probability of live birth of child B. It is also worth noting that in 70% of DET successful pregnancies only a single child is born (eg either child A_2 or child B_2). For the sake of simplicity we will ignore in

the rest of this table differences in the probabilities of live birth and assume that transferred embryos will result in live birth.

X - In this column a person affecting harm is listed for individuals who are worse off than they would have been had SET been adopted instead. This harm is indicated by the difference in wellbeing between different counterfactual states. A_2-A_1 refers to the difference in wellbeing attributable to being born as part of a twin rather than singleton pregnancy

Y - In this column, individuals are listed if they have lower wellbeing than individuals who would have existed if SET had been used. The difference in wellbeing is indicated as above

Z - In this column, additional individuals are listed who would not exist if SET had been used.

Theory*	Elements of view			DET vs SET	Pareto optimal policy (of options evaluated)
	PA Harm	Imp Harm	Impersonal (existential) benefit		
Narrow Person-affecting Principle	Yes	No	No	SET	SubDET, SET, repeatSET^2
No difference view (same number quality)	Yes	Yes	No	SET	SET, repeatSET^2
Person-affecting priority view	Yes	(Yes)	No	SET	SET, repeatSET^2
Wide person-affecting principle	Yes	Yes	Yes	DET	repeatSET^2

Appendix table 2: Implications of different views of person-affecting and impersonal harms for embryo transfer policy

The table focuses on harms/benefit for children born as a result of the different policies. The final column sets out which of the four policies represent the least harm from the different theoretical perspectives.

PA = Person-affecting

Imp = Impersonal

*These theories are adapted from Parfit, with the exception of the Person-affecting Priority View. This latter refers to a view that impersonal harms count, but are less significant than person-affecting harms (see main text)

REFERENCES

1. European Society of Human Reproduction and Embryology. 2012. 5 million babies. http://www.eshre.eu/sitecore/content/Home/Press Room/Press releases/Press releases ESHRE 2012/5 million babies. Accessed 3/1/2014.
2. European Society of Human Reproduction and Embryology. 2013. ART Fact Sheet. http://www.eshre.eu/Guidelines-and-Legal/ART-fact-sheet.aspx. Accessed 3/1/2014.
3. The Multiple Births Foundation. 2013. One at a Time. http://www.oneatatime.org.uk/index.htm. Accessed 3/1/2014.
4. Thurin, Ann, Jon Hausken, Torbjörn Hillensjö, Barbara Jablonowska, Anja Pinborg, Annika Strandell, and Christina Bergh. 2004. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *The New England journal of medicine* 351 (23):2392-2402. doi:10.1056/NEJMoa041032.
5. Peeraer, K, S Debrock, A Laenen, P De Loecker, C Spiessens, D de Neubourg, and T M D'Hooghe. 2013. The impact of legally restricted embryo transfer and reimbursement policy on cumulative delivery rate after treatment with assisted reproduction technology. *Human Reproduction*. doi:10.1093/humrep/det405.
6. Fauser, B. C., P. Devroey, and N. S. Macklon. 2005. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 365 (9473):1807-1816. doi:10.1016/S0140-6736(05)66478-1.

7. Maheshwari, Abha, Siriol Griffiths, and Siladitya Bhattacharya. 2011. Global variations in the uptake of single embryo transfer. *Human Reproduction Update* 17 (1):107-120. doi:10.1093/humupd/dmq028.
8. Bissonnette, F, S J Phillips, J Gunby, H Holzer, N Mahutte, P St-Michel, and I J Kadoch. 2011. Working to eliminate multiple pregnancies: a success story in Québec. *Reproductive BioMedicine Online* 23 (4):500-504. doi:10.1016/j.rbmo.2011.05.020.
9. Criteria for number of embryos to transfer: a committee opinion. 2013. *Fertility and Sterility* 99 (1):44-46. doi:10.1016/j.fertnstert.2012.09.038.
10. Human Fertilisation and Embryology Authority. 2011. Improving outcomes for fertility patients: multiple births. http://www.hfea.gov.uk/docs/2011-12-01_-_Multiple_Births_Publication_2011_-_Rationalising_Register_Data_-_FINAL_1.2.DOC.pdf. Accessed 2/1/2014.
11. Midland Fertility Services. 2014. Embryo Transfer Policy. http://www.midlandfertility.com/investigations-and-treatments/treatments/embryo-transfer-policy/. Accessed 16/07/2014.
12. Van Voorhis, Brad, E D Levens, and M J Hill. 2013. Should single-embryo transfer be mandatory in patients undergoing IVF? Contemporary Ob Gyn. Contemporary Ob/Gyn. http://contemporaryobgyn.modernmedicine.com/contemporary-obgyn/news/should-single-embryo-transfer-be-mandatory-patients-undergoing-ivf?contextCategoryId=26. Accessed 3/1/2014.
13. Janvier, A., B. Spelke, and K. J. Barrington. 2011. The epidemic of multiple gestations and neonatal intensive care unit use: the cost of irresponsibility. *J Pediatr* 159 (3):409-413. doi:10.1016/j.jpeds.2011.02.017.
14. Van Voorhis, Bradley J. 2007. Clinical practice. In vitro fertilization. *The New England journal of medicine* 356 (4):379-386. doi:10.1056/NEJMcp065743.
15. Human Fertilisation and Embryology Authority. 2009. IVF - chance of success. http://www.hfea.gov.uk/ivf-success-rate.html. Accessed 3/1/2014.
16. McLernon, D J, K Harrild, C Bergh, M J Davies, D de Neubourg, J C M Dumoulin, J Gerris et al. . 2010. Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials. *British Medical Journal* 341:c6945. doi:10.1136/bmj.c6945.
17. Kjellberg, Ann Thurin, Per Carlsson, and Christina Bergh. 2006. Randomized single versus double embryo transfer: obstetric and paediatric outcome and a cost-effectiveness analysis. *Human reproduction (Oxford, England)* 21 (1):210-216. doi:10.1093/humrep/dei298.
18. Lawlor, Debbie A, and Scott M Nelson. 2012. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: a prospective study. *Lancet* 379 (9815):521-527. doi:10.1016/S0140-6736(11)61267-1.
19. Sullivan, Elizabeth A, Yueping A Wang, Irene Hayward, Georgina M Chambers, Peter Illingworth, John McBain, and Robert J Norman. 2012. Single embryo transfer reduces the risk of perinatal mortality, a population study. *Human Reproduction* 27 (12):3609-3615. doi:10.1093/humrep/des315.
20. Pinborg, Anja, Anne Loft, Lone Schmidt, Gorm Greisen, Steen Rasmussen, and Anders Nyboe Andersen. 2004. Neurological sequelae in twins born after assisted conception: controlled national cohort study. *British Medical Journal* 329 (7461):311. doi:10.1136/bmj.38156.715694.3A.
21. Adegbite, A. L., S. Castille, S. Ward, and R. Bajoria. 2004. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. *American journal of obstetrics and gynecology* 190 (1):156-163. doi:10.1016/j.ajog.2003.07.004.

22. Cheang, C. U., L. S. Huang, T. H. Lee, C. H. Liu, Y. T. Shih, and M. S. Lee. 2007. A comparison of the outcomes between twin and reduced twin pregnancies produced through assisted reproduction. *Fertility and Sterility* 88 (1):47-52. doi:10.1016/j.fertnstert.2006.11.084.
23. Geva, E., L. Lerner-Geva, Z. Stavorovsky, B. Modan, L. Freedman, A. Amit, I. Yovel, and J. B. Lessing. 1998. Multifetal pregnancy reduction: a possible risk factor for periventricular leukomalacia in premature newborns. *Fertility and Sterility* 69 (5):845-850.
24. Grady, Rosheen, Nika Alavi, Rachel Vale, Mohammad Khandwala, and Sarah D McDonald. 2012. Elective single embryo transfer and perinatal outcomes: a systematic review and meta-analysis. *Fertility and Sterility* 97 (2):324-331. doi:10.1016/j.fertnstert.2011.11.033.
25. Sazonova, Antonina, Karin Källén, Ann Thurin-Kjellberg, Ulla-Britt Wennerholm, and Christina Bergh. 2013. Neonatal and maternal outcomes comparing women undergoing two in vitro fertilization (IVF) singleton pregnancies and women undergoing one IVF twin pregnancy. *Fertility and Sterility* 99 (3):731-737. doi:10.1016/j.fertnstert.2012.11.023.
26. Fiddelers, A A A, J L Severens, C D Dirksen, J C M Dumoulin, J A Land, and J L H Evers. 2007. Economic evaluations of single- versus double-embryo transfer in IVF. *Human Reproduction Update* 13 (1):5-13. doi:10.1093/humupd/dml053.
27. Scotland, G S, D McLernon, J J Kurinczuk, P McNamee, K Harrild, H Lyall, M Rajkhowa, M Hamilton, and S Bhattacharya. 2011. Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost-utility of elective single versus double embryo transfer over a 20-year time horizon. *BJOG: An International Journal of Obstetrics and Gynaecology* 118 (9):1073-1083. doi:10.1111/j.1471-0528.2011.02966.x.
28. Mill, John Stuart. 2011. *On Liberty*. Luton: Andrews UK Limited.
29. Roberts, Stephen A, Linda McGowan, Andy Vail, and Daniel R Brison. 2011. The use of single embryo transfer to reduce the incidence of twins: Implications and questions for practice from the 'towardSET?' project. *Human Fertility* 14 (2):89-96. doi:10.3109/14647273.2011.568037.
30. Leese, Brenda, and Jane Denton. 2010. Attitudes towards single embryo transfer, twin and higher order pregnancies in patients undergoing infertility treatment: a review. *Human Fertility* 13 (1):28-34. doi:10.3109/14647270903586364.
31. Pinborg, Anja, Anne Loft, Lone Schmidt, and Anders Nyboe Andersen. 2003. Attitudes of IVF/ICSI-twin mothers towards twins and single embryo transfer. *Human reproduction (Oxford, England)* 18 (3):621-627. doi:10.1093/humrep/deg145.
32. Chambers, Georgina M, Elizabeth A Sullivan, Osamu Ishihara, Michael G Chapman, and G David Adamson. 2009. The economic impact of assisted reproductive technology: a review of selected developed countries. *Fertility and Sterility* 91 (6):2281-2294. doi:10.1016/j.fertnstert.2009.04.029.
33. Verberg, M. F., M. J. Eijkemans, E. M. Heijnen, F. J. Broekmans, C. de Klerk, B. C. Fauser, and N. S. Macklon. 2008. Why do couples drop-out from IVF treatment? A prospective cohort study. *Human reproduction (Oxford, England)* 23 (9):2050-2055. doi:10.1093/humrep/den219.
34. Thurin-Kjellberg, Ann, Catharina Olivius, and Christina Bergh. 2009. Cumulative live-birth rates in a trial of single-embryo or double-embryo transfer. *The New England journal of medicine* 361 (18):1812-1813. doi:10.1056/NEJMc0907289.
35. Dworkin, G. 1983. Comment on Narveson: in defense of equality. *Social Philosophy and Policy* 1:28-40.
36. Paris, J. J. 2010. Autonomy does not confer sovereignty on the patient: a commentary on the Golubchuk case. *American Journal of Bioethics* 10 (3):54-56.
37. Paris, J J, M D Schreiber, M Statter, R Arensman, and M Siegler. 1993. Beyond autonomy--physicians' refusal to use life-prolonging extracorporeal membrane oxygenation. *New England Journal of Medicine* 329 (5):354-357. doi:10.1056/NEJM199307293290512.
38. Berg, Jessica Wilen. 2005. Owning Persons: The Application of Property Theory to Embryos and Fetuses. *Wake Forest Law Review* 40:04-16.

39. Goold, Imogen. 2014. Why does it matter how we regulate the use of human body parts? *Journal of Medical Ethics* 40 (1):3-9. doi:10.1136/medethics-2012-100941.
40. Wilkinson, Stephen. 2003. *Bodies for sale : ethics and exploitation in the human body trade*. London: Routledge.
41. Dickens, B. M., and R. J. Cook. 2010. The legal status of in vitro embryos. *Int J Gynaecol Obstet* 111 (1):91-94. doi:10.1016/j.ijgo.2010.07.004.
42. Stillman, Robert J, Kevin S Richter, and Howard W Jones. 2013. Refuting a misguided campaign against the goal of single-embryo transfer and singleton birth in assisted reproduction. *Human reproduction (Oxford, England)* 28 (10):2599-2607. doi:10.1093/humrep/det317.
43. Ryan, Ginny L, Amy E T Sparks, Christopher S Sipe, Craig H Syrop, Anuja Dokras, and Bradley J Van Voorhis. 2007. A mandatory single blastocyst transfer policy with educational campaign in a United States IVF program reduces multiple gestation rates without sacrificing pregnancy rates. *Fertility and Sterility* 88 (2):354-360. doi:10.1016/j.fertnstert.2007.03.001.
44. Liu, Shiliang, Robert M Liston, K S Joseph, Maureen Heaman, Reg Sauve, Michael S Kramer, and Maternal Health Study Group of the Canadian Perinatal Surveillance System. 2007. Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. *CMAJ: Canadian Medical Association Journal* 176 (4):455-460. doi:10.1503/cmaj.060870.
45. Wiklund, Ingela, Gunnar Edman, and Ellika Andolf. 2007. Cesarean section on maternal request: reasons for the request, self-estimated health, expectations, experience of birth and signs of depression among first-time mothers. *Acta Obstetricia et Gynecologica Scandinavica* 86 (4):451-456. doi:10.1080/00016340701217913.
46. Diekema, D. S. 2004. Parental refusals of medical treatment: the harm principle as threshold for state intervention. *Theoretical Medicine and Bioethics* 25 (4):243-264.
47. Bandolier. 2008. Risk of death and transportation. http://www.medicine.ox.ac.uk/bandolier/booth/Risk/trasnsportpop.html. Accessed 5/1/2014.
48. Dawson, A. 2005. The determination of the best interests in relation to childhood immunisation. *Bioethics* 19 (1):72-89.
49. Parfit, D. 1984. *Reasons and persons*. Oxford: Oxford University Press.
50. Stylianou, C., D. Critchlow, D. R. Brison, and S. A. Roberts. 2012. Embryo morphology as a predictor of IVF success: an evaluation of the proposed UK ACE grading scheme for cleavage stage embryos. *Hum Fertil (Camb)* 15 (1):11-17. doi:10.3109/14647273.2011.652251.
51. Illmensee, Karl, Mike Levanduski, Andrea Vidali, Nabil Husami, and Vasilios T Goudas. 2010. Human embryo twinning with applications in reproductive medicine. *Fertility and Sterility* 93 (2):423-427. doi:10.1016/j.fertnstert.2008.12.098.
52. [redacted]
53. Harris, J. 2000. Is there a coherent social conception of disability? *Journal of Medical Ethics* 26 (2):95-100. doi:10.1136/jme.26.2.95.
54. Bennett, Rebecca. 2013. When Intuition is Not Enough. Why the Principle of Procreative Beneficence Must Work Much Harder to Justify Its Eugenic Vision. *Bioethics*. doi:10.1111/bioe.12044.
55. McMahan, J. 2012. Causing People to Exist and Saving People's Lives. *The Journal of Ethics*:1-31. doi:10.1007/s10892-012-9139-1.
56. [redacted]
57. [redacted]

58. Bromer, Jason G, Baris Ata, Meltem Seli, Charles J Lockwood, and Emre Seli. 2011. Preterm deliveries that result from multiple pregnancies associated with assisted reproductive technologies in the USA: a cost analysis. *Current Opinion in Obstetrics & Gynecology* 23 (3):168-173. doi:10.1097/GCO.0b013e32834551cd.
59. Connolly, M, F Gallo, S Hoorens, and W Ledger. 2009. Assessing long-run economic benefits attributed to an IVF-conceived singleton based on projected lifetime net tax contributions in the UK. *Human reproduction (Oxford, England)* 24 (3):626-632. doi:10.1093/humrep/den435.
60. Connolly, M. P., M. S. Pollard, S. Hoorens, B. R. Kaplan, S. P. Oskowitz, and S. J. Silber. 2008. Long-term economic benefits attributed to IVF-conceived children: a lifetime tax calculation. *The American Journal of Managed Care* 14 (9):598-604.
61. Davis, Lynn B, Sara J Champion, Steve O Fair, Valerie L Baker, and Alan M Garber. 2010. A cost-benefit analysis of preimplantation genetic diagnosis for carrier couples of cystic fibrosis. *Fertility and Sterility* 93 (6):1793-1804. doi:10.1016/j.fertnstert.2008.12.053.
62. Avraham, S., and D. S. Seidman. 2012. The multiple birth epidemic: revisited. *Journal of Obstetrics and Gynaecology of India* 62 (4):386-390. doi:10.1007/s13224-012-0309-7.
63. Stillman, Robert J, Kevin S Richter, Nicole K Banks, and James R Graham. 2009. Elective single embryo transfer: a 6-year progressive implementation of 784 single blastocyst transfers and the influence of payment method on patient choice. *Fertility and Sterility* 92 (6):1895-1906. doi:10.1016/j.fertnstert.2008.09.023.
64. Chambers, Georgina M, Peter J Illingworth, and Elizabeth A Sullivan. 2011. Assisted reproductive technology: public funding and the voluntary shift to single embryo transfer in Australia. *The Medical journal of Australia* 195 (10):594-598. doi:10.5694/mja10.11448.
65. Jain, Tarun, Bernard L Harlow, and Mark D Hornstein. 2002. Insurance coverage and outcomes of in vitro fertilization. *The New England journal of medicine* 347 (9):661-666. doi:10.1056/NEJMsa013491.
66. Manninen, B A. 2011. Parental, medical, and sociological responsibilities:“Octomom” as a case study in the ethics of fertility treatments. *Journal of Clinical Research & Bioethics* 1:2. doi:10.4172/2155-9627.S1-002.
67. Luke, B., M. B. Brown, J. E. Stern, D. A. Grainger, N. Klein, and M. Cedars. 2010. Effect of embryo transfer number on singleton and twin implantation pregnancy outcomes after assisted reproductive technology. *J Reprod Med* 55 (9-10):387-394.