

Fetal therapy for Down syndrome

Citation for published version (APA):

de Wert, G., Dondorp, W., & Bianchi, D. W. (2017). Fetal therapy for Down syndrome: an ethical exploration. *Prenatal Diagnosis*, 37(3), 222-228. <https://doi.org/10.1002/pd.4995>

Document status and date:

Published: 01/03/2017

DOI:

[10.1002/pd.4995](https://doi.org/10.1002/pd.4995)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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ORIGINAL ARTICLE

Fetal therapy for Down syndrome: an ethical exploration

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ABSTRACT

Background Parallel to recent advances in prenatal screening for Down syndrome (DS), therapies for different aspects of the condition have become available. As intellectual disability is a key aspect, this is an active area for research. Several groups have hypothesized that prenatal interventions will give better chances at improving cognitive functioning in persons with DS than postnatal treatment. Clinical trials are being developed.

Method We first discuss the ethical pros and cons of trying to improve cognitive functioning in persons with DS to see if there are categorical objections to the general idea, and then move on to explore ethically relevant aspects of the prospect of developing fetal therapy for DS (FTDS).

Results Only on the basis of a one-dimensional emphasis on the social model of disability would (fetal) therapy aimed at cognitive improvement be inherently problematic.

Conclusions Inviting pregnant women to participate in FTDS-research should be based on adequate pre-clinical trials, as well as information aimed at avoiding the so-called 'therapeutic misconception'. Should FTDS be proven to be effective and safe, women carrying a fetus with trisomy 21 who have decided to continue the pregnancy may have a moral obligation to make use of this option. © 2016 John Wiley & Sons, Ltd.

Funding sources: None declared

Conflicts of interest: Dr. Bianchi's contribution to this work was conducted while she was employed at Tufts Medical Center. It does not necessarily reflect the views of the United States Government or the National Institutes of Health.

INTRODUCTION

In many countries worldwide, prenatal screening for Down syndrome (DS) has been available for decades. The recent introduction of maternal plasma cell-free DNA sequencing for DS, also known as 'non-invasive prenatal testing' (NIPT), is widely appreciated as a major advance, as it detects around 97% of cases of trisomy 21 with a very low false positive rate as early as 10 weeks of gestation.^{1,2} Importantly, with NIPT the positive predictive value (PPV) of a positive screen for trisomy 21 is 10- to 20-fold higher than current techniques of biochemical analyte and nuchal translucency measurements.^{3,4}

In parallel, over the last few decades, medical and surgical therapies for different aspects of DS have become available, and there is wide interest in their further development and improvement. While therapies for DS are starting to become integrated into postnatal care, there is a growing interest in the development of fetal (prenatal, *in utero*) therapy (FTDS), as part of a 'fetal personalized medicine' strategy.⁵ This approach may be more effective than waiting until after birth, particularly when it comes to neurocognitive FTDS aimed at

improving the future child's intellectual development and independent life skills.⁶ It is hoped and expected that such therapy, if effective, could become an option for pregnant women carrying a fetus with trisomy 21, and presented as part of post-test counseling.

While research on neurocognitive FTDS is still mainly in the pre-clinical stage, a pro-active ethical debate is needed, as such research, and the possible future integration of FTDS into clinical care, raises complex normative questions, both substantive and procedural. The main question of this article is as follows: is neurocognitive FTDS ethically justified or even desirable, and if so, under what conditions?

CURRENT AND FUTURE TREATMENTS FOR DOWN SYNDROME

Until a few decades ago, DS was considered an untreatable condition. Many babies with DS died because of severe congenital heart or intestinal anomalies, and those who survived were often institutionalized. This picture has changed remarkably, as in most countries; it is now typical for affected

children to be raised by their families and to attend public schools.⁷

Postnatal treatments for Down syndrome

Current standards of care

At the present time, all therapies only address the symptoms of DS; they do not remove the extra copy of chromosome 21. In the United States and other developed countries, there are clear guidelines to aid pediatricians who provide primary care for infants and children with DS.⁸ These include confirmation of prenatal genetic diagnostic tests, annual audiology and ophthalmology examinations, annual hemoglobin and thyroid stimulation hormone (TSH) screening, echocardiography studies and a cardiology consultation, and a sleep study by the age of 4 years due to the increased incidence of sleep apnea.⁹ It is expected that any abnormalities detected during these examinations will be treated as they would for any child without DS. For example, 50% of infants with DS have congenital heart disease and 12% have gastrointestinal atresias.⁸ These are treated with surgical repair. Fifty per cent of children with DS have refractive errors, and they are treated with corrective lenses.

Clinical research

Abnormalities in virtually every organ system, except the brain, are routinely treated in DS. Intellectual disability, however, is a key aspect of the condition. While not every person with DS (or parent of a child with DS) wishes to pursue neurocognitive treatment, this is certainly an active area of clinical research. In general, the goal is to raise a person's intellectual quotient (IQ) to facilitate improvement in independent living skills. To date, nine different molecules have been tested in adult and adolescent clinical trials (as reviewed in Guedj et al. 2014¹⁰). These include the acetyl cholinesterase inhibitors donepezil and rivastigmine, the choline pathway enhancer piracetam, a glutamate receptor (NMDAR) antagonist, memantine, human growth hormone, folic acid, vitamin E, the DYRK1A inhibitor epigallocatechin gallate (EGCG), and a gamma butyric acid receptor antagonist known as RG1662. While two of these molecules (EGCG and piracetam) have demonstrated limited clinical benefits, the majority has not shown statistically significant improvement in treated individuals. This is in part, possibly because the treatments are being administered too late in life.

Future approaches

As stated earlier, there is no 'comprehensive' therapy for DS, meaning that all of the signs and symptoms of the condition will be eliminated. It is uncertain that there will ever be one. Yet, a relatively recent basic science study explored the possibility that the extra copy of chromosome 21 could be 'silenced' in an *in vitro* model system.¹¹ By inactivating the third copy of chromosome 21, Jiang and colleagues demonstrated that they could get normal development to proceed. This study received much attention in the scientific and lay press, with *The Guardian* commenting, 'Although full treatment is still many years off, the work will drive the research for therapies that improve common symptoms of

DS.¹² However, while this approach is feasible in cell culture, there will be major difficulties in translating this to developing human embryos.

Fetal therapy for Down syndrome

Until recently, little attention has been paid to the brain phenotype in fetuses with DS. Deviation from typical fetal development starts to occur by the second trimester, as demonstrated by sonographic examinations,^{13,14} magnetic resonance examinations,¹⁵ and studies of brain-derived cell-free RNA in amniotic fluid supernatant.¹⁶ Several groups have hypothesized that prenatal will be more effective than postnatal neurocognitive treatment because neuronal progenitor cells die *in utero* in fetuses with DS; if this can be reversed it will lead to more typical brain growth and intercellular wiring.^{6,17} If safe and effective, FTDS may revolutionize the concept and practice of prenatal screening for DS. In this scenario, NIPT would create a 'window of opportunity' for FTDS.^{5,17}

Standard of care

Following a prenatal diagnosis of trisomy 21, the standard of care is for the expectant couple to undergo post-test counseling, ideally by someone with knowledge of contemporary outcomes for children with DS. In one study that compared outcomes between 21 women who had prenatal diagnosis and continued the pregnancy versus 17 women who received their child's diagnosis at birth,¹⁸ multiple benefits of prenatal diagnosis were shown. These included the chance to prepare educationally and psychologically for the birth of their child, meeting the pediatric subspecialists who would care for their child once born, and the opportunity to deliver at a tertiary medical center where they would not be separated from their infant.

Clinical research

Based on data from studies in DS mouse models suggesting improved brain growth following prenatal or neonatal exposure to the selective serotonin reuptake inhibitor antidepressant fluoxetine (Prozac),^{19,20} a team at the University of Texas Southwestern Medical Center is enrolling 21 pregnant women whose fetuses have been diagnosed with trisomy 21 into a clinical study comparing maternal administration of fluoxetine ($N=14$) to a placebo control ($N=7$).²¹ After birth, the infants will continue treatment or placebo up until 2 years of age. Study participants will undergo regular behavioral testing and magnetic resonance imaging to measure brain size and evaluate anatomical landmarks.

Future approaches

Although there is some controversy regarding which mouse models best represent the clinical phenotype in humans with DS, an extensive integrated analysis of human and murine dysregulated transcriptomes and pathways is currently underway.²² Data have been acquired from amniocytes from living human fetuses with trisomy 21, and age and sex-matched euploid controls, as well as embryonic day 15.5 forebrains from three different mouse models of DS (Ts1Cje,

Ts65Dn, and Dp16). Gene expression data have been uploaded into the Connectivity Map (www.broadinstitute.org/CMaP) database to identify safe drugs that are approved by the United States Food and Drug Administration and would be expected to reverse the abnormal embryonic brain phenotype. The CMap analyses have identified 56 candidate molecules with high predictive scores to rescue abnormal gene expression in both mice and humans.²² Additional preclinical studies include administration of EGCG and/or choline supplementation to pregnant dams carrying embryos with model forms of DS. While murine and human brains develop differently, these preclinical studies are important to demonstrate safety and efficacy of various therapies. It is anticipated that human clinical trials will begin within the next 5 years, although it should be noted that pregnant women carrying fetuses with DS are already taking supplements and medications outside of the traditional medical mainstream.

ETHICS OF (FETAL) NEUROCOGNITIVE THERAPY FOR DOWN SYNDROME

In this section, we will first argue that the development of neurocognitive therapy for DS is ethically desirable. Secondly, we will defend the ethical acceptability of moving this therapy to the prenatal period. As this will be a discussion on general pros and cons, nothing will be written about the conditions for the responsible development and introduction of this new form of fetal therapy. We will address that further question in the next section.

Ethics of therapy for Down syndrome

In a survey among parents of children with DS, Canadian researchers explored how they would perceive the possible availability of (postnatal) treatment that would mitigate the intellectual disability associated with DS.²³ They found that parental attitudes toward such a scenario were complex and affected by different and sometimes conflicting ethical considerations. Most respondents supported the statement that reducing intellectual disability in individuals affected with DS would be a good thing. However, only a smaller proportion would want to use this for their own child. Arguments in support of neurocognitive treatment focused on enhanced independence and improved quality of life both for the child and the family.

Ethically, these arguments can be accounted for in terms of beneficence, autonomy, and justice. Beneficence is served because raising their IQ will enable people with DS to have more control over their own lives, thus also taking away what they may experience as a source of frustration.²⁴ The ability to reason may either be regarded as a 'general purpose means' necessary for all possible life plans²⁵ or as an essential part of human flourishing.²⁶ On the latter perspective, promoting a person's autonomy is a morally worthwhile aim in itself. Moreover, the parents also considerably benefit from being freed from the responsibilities related to their child's life-long dependence and concerns about who will take care of the child when they are no longer around.²⁷ Finally, the removal of barriers to equal opportunities due to a disorder or handicap can be regarded as a requirement of justice.²⁸ The reasoning

being that if justice requires compensating inequalities of opportunity that result from disabilities, it also provides a ground for efforts aimed at taking away the cause of those inequalities.

In addition to potentially benefitting children with DS and their parents, the availability of effective neurocognitive treatment may have the further benefit of giving more options for reproductive choice to pregnant women (and their partners), when found to be carrying a fetus with trisomy 21. Especially for those in whom the choice between having a child with an intellectual disability and terminating the pregnancy is a real dilemma, it might make an important difference to know that with early treatment the cognitive functioning of their child can be significantly improved.

The idea of developing neurocognitive treatment for DS also raises ethical concerns among parents of children with DS.²³ Part of these relate to what has been called the social model of disability. While the traditional medical model understands handicap or impairment in both medico-biological and individual terms, the social model focuses on socio-cultural structures that are behind the barriers to equal participation of people with impairments.^{29,30} This perspective suggests that if anything is in need of change, it is not people with DS, but society's failure to properly support them. The social-model perspective is behind the so-called 'expressivist' critique of prenatal testing for DS and other congenital abnormalities.³¹ The offer of such testing would send the message that the lives of people with disabilities are burdens to society that can best be avoided through timely diagnosis and selective abortion. Building on this, some might argue that the provision of neurocognitive treatment would send a similar message of not accepting people with DS as they are. A related argument is that people with DS contribute to diversity, and that this is to be regarded as something valuable for society as a whole.

Moreover, some parents of children with DS see their disability as an occasion for their own moral growth.²⁴ Finally, treatment would not just change some disease-related features, but it would affect the individual's personality. This leads to the question as to what extent such treatment could be regarded a benefit to that person?

Reflecting on these considerations, we do not think that ethically, it would be wrong to try to develop neurocognitive treatment for DS. It is certainly true that at least part of the problems that people with disabilities such as DS encounter could be avoided or diminished if society were more inclusive of diversity. To the extent that this social dimension is neglected in the medical model of disability, it is indeed one-sided. But the same goes for the social model, in so far as it reduces the problems of people with DS to prejudice and exclusion. The two models should be regarded as complementary rather than mutually exclusive.²⁹ Ignoring this, the 'expressivist' critique fails to acknowledge that pregnant women and their partners may have morally sound reasons for wanting to avoid the birth of a child with DS and that enabling this choice through prenatal testing does not in itself presuppose a negative view of the value of the life of people with DS. Nor is such a view necessarily implied in the idea of neurocognitive treatment. Moreover, as there are plenty of

other opportunities that give cause for celebrating societal diversity and for pursuing moral growth as individuals and parents, these ideals should not be regarded as standing in the way of trying to improve the quality of life of people with DS by means of medical interventions. To the extent that the 'change of personality' argument is indeed more convincing, it is only so with regard to neurocognitive treatment of individuals whose personalities have already been formed. In fact, several respondents in the Canadian study said they might have considered treatment for DS 'at or before birth' when their child's personality was still to be formed, but not later in his or her life.²³

Ethics of fetal therapy for Down syndrome

As there are strong ethical reasons for developing neurocognitive treatment for DS and as there do not seem to be overriding objections, the question arises what this would mean for the development of FTDS? As explained above, an important reason for making the step to the prenatal period is its hypothesized greater effectiveness. If, by treating DS prenatally, a greater increase in IQ can be obtained than with postnatal therapies, then in principle, this would be an argument for preferring FTDS. Secondly, in addition to avoiding the 'change of personality' objection by treating before birth, FTDS may have a psychological advantage over postnatal treatment for the parents, as the child will already be born with better neurocognitive capacities. Third, if FTDS is indeed more effective than postnatal treatment, this approach might create an additional option for pregnant women and their partners. However, the ethics of this last point can be analyzed in different ways that need to be carefully distinguished.

From a 'fetalist' perspective, the development of FTDS may be welcomed as making abortion of fetuses with trisomy 21 unnecessary. In fact, this is in line with how the aim of prenatal diagnosis was understood by Jérôme Lejeune, the French pediatrician and geneticist credited with the discovery of the chromosomal basis of Down syndrome.³² Others have also stated that the development of safe and effective fetal therapy belongs to the 'ultimate goals' of prenatal diagnosis.³³ As such, this seems an ideal that no one could reasonably criticize. However, to the extent that it hinges on an understanding that fetuses are patients who have a right to be treated, it may connect to a 'pro-life' agenda that denies women the right to abortion. Whereas it should be welcomed that FTDS gives women a further choice, presenting this as the morally preferred option would be ethically problematic, given the contested nature of the underlying view of the status of the fetus.

From a liberal ('pro-choice') perspective, the development of this alternative is to be welcomed as in line with the very aim of prenatal testing, understood as serving reproductive autonomy by giving individual women or couples meaningful options for choice with regard to reproductive risks.^{34,35} However, it should be acknowledged that for some women or couples, abortion is unacceptable or even illegal. Even for many of those couples who are not categorically opposed to termination, deciding to end a wanted pregnancy remains an

extremely difficult choice that may have lifelong psychosocial consequences. And for those pregnant women who at present reject the offer of prenatal screening for DS because they would not consider a selective termination of a trisomy 21 pregnancy,³⁶ this may change with the availability of FTDS as an option. If proven effective and safe, FTDS would have the further benefit of allowing the practice of prenatal screening to better achieve its aim of facilitating autonomous reproductive choices.

The reasoning that FTDS would create an alternative option for reproductive choice that should neither be imposed upon women nor withheld from them, seems to closely connect with the ethos of professional non-directivity and respect for reproductive autonomy. However, as we will argue in the next section, this is only part of the story. Because if pregnant women carrying a fetus with trisomy 21 decide not to have an abortion but to carry the pregnancy to term, the availability of the new option of FTDS cannot be regarded as morally indifferent. As we will argue, the decision not to have an abortion creates a *prima facie* moral obligation to make use of FTDS, if indeed proven effective, beneficial and safe. Clearly, this is not without consequences for the ethics of reproductive counseling.

RESPONSIBLE DEVELOPMENT AND INTRODUCTION OF FETAL THERAPY FOR DOWN SYNDROME

All treatments aimed at the fetus, whether surgical or medical, also entail an intervention into the body of the pregnant woman. This means that fetal therapy, just like any other medical treatment proposed to the pregnant woman, requires her explicit consent. This is not to say that the role of fathers-to-be is not important, or that professionals should exclude them from the decision-making process.³⁷ In fact, most couples will want to make these decisions together, as they affect the future of both their child and their family. The point, however, is that fetal therapy involves the pregnant woman directly, as she will have medical or surgical interventions that make her a patient or research subject as well. That is something about which, both ethically and legally, only she can decide.

But consent is not enough to render the proposition ethical.³⁸ Some have argued that fetal therapy should only be considered if the risk to the health and well-being of the pregnant woman is negligible.³⁹ In our view, this is too strong. Given the interests at stake, particularly the woman's self-declared interest in giving birth to a healthy child as well as the health interests of the child-to-be, more than negligible risks may well be acceptable, as long as they are not disproportionate.⁴⁰

Ethics of research into fetal therapy for Down syndrome

Whereas the term 'therapy' may suggest established treatments, in fact many prenatal interventions are still experimental or investigational. In view of the need for adequate pre-clinical data from animal models demonstrating safety and efficacy, there is a concern that human trials for FTDS may have been started prematurely. Criteria originally developed for fetal surgery, but generally relevant, stipulate

that fetal interventions should only be carried out in specialized multidisciplinary fetal treatment centers following strict protocols that have been approved by a local ethics committee. They should only be considered if (1) the diagnosis is certain, (2) the natural history of the disorder is clearly understood, (3) there is no equally effective postnatal therapy, (4) there is compelling experimental evidence regarding safety and efficacy based on animal studies.⁴¹ There is currently much support in the field for introducing new fetal treatments in a clinical research setting, ideally using randomized controlled trials (RCTs) and evaluating long term effects in the children and their mothers.

As a general rule, because of the balance of risks and benefits, fetal therapy should only be considered if the disorder to be treated has been definitively diagnosed. For FTDS research studies this means that only pregnant women carrying a fetus with trisomy 21 based on a diagnostic test such as amniocentesis or CVS should be included. Inclusion should be limited to women (couples) who have already clearly decided that they want to keep the child.

Inviting women to participate in FTDS research should be based on adequate information aimed at avoiding the so-called 'therapeutic misconception,' by stressing that the research is being performed precisely because it is not yet known whether FTDS leads to better outcomes than doing nothing. What should also be made clear is that FTDS may lead to a better neurocognitive outcome in children with DS and should not be expected to provide a complete cure for the syndrome as a whole.

Follow-up: impact of fetal therapy for Down syndrome

Whether FTDS is successful ultimately depends not on the level of cognitive improvement, but on the extent to which it improves the lives of people with DS. This links with current research on self-esteem and social comparison in people with cognitive impairments.⁴² As negative social comparisons are found to be related to depression and psychopathology, FTDS can be expected to have a positive impact on the quality of life of people with DS. However, there are also hypothetical concerns about adverse effects. For instance, it can be asked if a partial improvement in cognitive functioning may make persons with DS only more aware of not being able to fully participate in society or to realize the professional and reproductive options that are open to others. They may also be more aware of the threat of developing early onset dementia, something that FTDS may or may not be able to avert. In this connection, an important issue is how any of these positive or negative effects are mediated by parental disclosure to the child of having had FTDS. Finally: to the extent that FTDS would bring the IQ of some people with DS into the typical range, they would still be physically recognizable as having DS. How would this affect their social functioning and acceptance?²³

Timing of fetal therapy for Down syndrome

Should FTDS become available as a possible option for women carrying a fetus with trisomy 21, an important issue concerns the best timing for the intervention. From a neurodevelopmental perspective, it may well be best to start treatment as early as possible (i.e., in the first trimester).⁶ This

would then increase pressure for early diagnosis and early decision-making as to whether to continue the pregnancy or have a termination. With CVS, a diagnosis of trisomy 21 can be obtained at 11 weeks. However, there are some concerns with pushing for early decision making. Firstly, at this stage of pregnancy there is a relatively high spontaneous fetal loss rate in trisomy 21. This not only means a relatively high rate of psychologically burdensome termination decisions for pregnancies that would otherwise not have led to a surviving infant, but also that women who decide to have FTDS at an early stage of pregnancy may turn out to have undergone that treatment 'for nothing'. Of course, how problematic that is would also depend on the eventual safety-profile of FTDS. Secondly, the push for an early choice may be at odds with the ideal of helping pregnant women to make well considered autonomous decisions about what to do with the pregnancy. Finally, additional information about related comorbidities (e.g., heart defects) that women or couples might regard as relevant for their decision-making may only become available later in pregnancy. Psychological research into how the availability and the timing of FTDS may affect the dynamics of reproductive decision-making will be needed to find out how best to answer these concerns.

Fetal therapy for Down syndrome: reproductive autonomy and parental responsibility

Given that the status of the fetus is a matter of irreconcilable world views, pregnant women should not be expected to expose themselves to possible risks in order to save the life of the fetus, not even after the potential for extra uterine viability has been achieved.⁴⁰ In so far, as we have argued above, there is no reason for moving away from the ethos of reproductive autonomy. However, several fetal therapies already incorporated into clinical care, such as the surgical correction of myelomeningocele *in utero*,⁴³ are not about saving the fetus, but about improving the health prospects of the future child. This would also be the case with FTDS. And whatever the status of the fetus, it is clear that the child-to-be, if it is allowed to be born, will indeed be or become a person, whose interests can already be harmed or furthered during pregnancy.⁴⁴⁻⁴⁶ Importantly, for the interests of the future child to count, it is irrelevant at what gestational age treatment would take place. Concerns that this would undermine the woman's right to have a termination are mistaken. For if she has an abortion, there will be no child whose interests can be harmed or promoted by her choices. But if she decides to carry the pregnancy to term, the interests of the future child should be a morally weighty consideration.

This may entail a certain degree of professional directiveness, in cases in which the woman would need to be reminded of her parental responsibility. This is not really different from directly counseling pregnant women to stop smoking or drinking alcohol. Of course, the moral scope for asking the pregnant woman to consider fetal therapy is constrained by the principle of proportionality. One should only think here of an accepted, evidence-based treatment that would save the future child from significant and irreversible damage, without exposing the pregnant woman to serious

burdens or risks.⁴⁰ Depending on the outcome of clinical trials, FTDS may well fit this profile.

CONCLUSIONS AND RECOMMENDATIONS

There are strong ethical reasons for developing neurocognitive prenatal treatment for DS. None of the possible concerns amounts to an overriding a priori objection.

If, with FTDS, a greater increase in IQ can be obtained, then in principle, this would be an argument for preferring FTDS over postnatal therapies.

If safe and effective, FTDS will give pregnant women carrying a fetus with trisomy 21 an additional reproductive option that allows them a 'third path' to avoid the dilemma between having a termination or giving birth to a child with intellectual disabilities.

The aim of FTDS is not to protect the fetus against abortion, but to further the reproductive interests of prospective parents and the interests of their future child.

As a form of fetal therapy, FTDS entails an intervention into the body of the body of the pregnant woman that requires her informed consent. That can only be ethical on the basis of scientific evidence that the treatment is more effective than no treatment, and that the risks and burdens are not disproportionate.

Inviting pregnant women to participate in FTDS-research should be based on adequate pre-clinical trials, as well as information aimed at avoiding the so-called 'therapeutic misconception'. To avoid decision-regret, inclusion should be limited to those who have already clearly decided that they want to continue the pregnancy. If pregnant women carrying a fetus with trisomy 21 decide to continue the pregnancy, this may create a *prima facie* moral obligation to make use of FTDS, if indeed proven effective and safe. This also may require a reconsideration of the ethics of reproductive counseling, allowing for some degree of professional directivity with regard to choices that are not morally indifferent.

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Outcomes research will be necessary to determine if FTDS results in improvements in the quality of life for people with DS. Lastly, If FTDS is safe and effective, psychosocial research will also be needed to see how the availability and the timing of this treatment may affect the dynamics of reproductive decision-making by pregnant women and their partners.

ACKNOWLEDGEMENTS

The authors are grateful to Mr. Mark Bradford and Dr. Faycal Guedj for their critical reading of the manuscript and their helpful suggestions.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- An extensive integrated analysis of human and murine dysregulated transcriptomes and pathways is currently underway. Candidate molecules have been identified with high predictive scores to reverse the abnormal embryonic brain phenotype in both mice and humans.
- Parents of children with DS were found to have complex and diverging attitudes with regard to the desirability of treatment aimed at improving cognitive functioning.

WHAT DOES THIS STUDY ADD?

- There are strong ethical reasons for developing neurocognitive treatment for DS.
- The aim of fetal treatment for DS is not to protect the fetus against abortion, but to further the reproductive interests of prospective parents and the interests of their future child.
- If safe and effective, fetal treatment for DS will give a pregnant woman carrying a fetus with trisomy 21 an additional reproductive option.

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