Early Human Development 196 (2024) 106072

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Egg donation and gestational surrogacy: Pregnancy is riskier with an unrelated embryo

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ARTICLE INFO

Keywords:
Surrogacy
Gestational carrier
Egg donation
Egg donor
Ova donor
Oocyte donor
IVF
Immunology
Pregnancy
Microchimerism
Evolutionary medicine
Allogeneic pregnancies
Shared motherhood
Embryo donation

ABSTRACT

Modern medicine has revolutionized family planning. Remarkably, women[1] can carry to term embryos with whom they share no genetic connection, a feat made possible through egg donation and/or gestational surrogacy. Our reproductive systems evolved to accommodate embryos that are 50% related to the carrier, not 0% related. Here, we apply evolutionary theory to explain how and why pregnancy is riskier with an unrelated embryo. When a woman gestates an unrelated embryo, she is significantly more likely to develop preeclampsia and other diseases above and beyond the known risks associated with advanced maternal age, IVF, multiple gestation, and subfertility. Such "allogeneic pregnancies" are riskier even in fertile, healthy, commercial surrogates and when the egg is donated by a young, healthy donor. We propose that unrelated embryos present a special immune challenge to the gestational carrier, because they have fewer matching genes to the maternal body—therefore exacerbating symptoms of evolutionary maternal-fetal conflict. Indeed, maternal risks seem lower when the embryo is more related to the carrier, e.g., if a sister donates the egg. Finally, we discuss microchimerism in egg donation pregnancies, whereby wholly foreign cells pass from mother to embryo and vice-versa. We conclude with several medical proposals. First, egg donors and surrogates should be informed of the increased health risks they would face. In considerations of risk, these young, fertile women should not be compared to older, infertile women undergoing IVF; the proper comparison group is other young, fertile women. Second, contrary to some medical advice, perhaps genetically-related egg donors and surrogates should be preferred, all else equal. An immunological matching scheme, like what is used for organ transplants, could improve surrogate pregnancy outcomes. Third, more research is needed on microchimerism, sperm exposure, and the long-term impacts of allogeneic pregnancies on maternal and child health.

1. Introduction

Modern fertility medicine can produce outcomes that were once considered impossible. Since the 1980s, the use of assisted reproductive technologies (ART) has increased dramatically, sometimes with impressive results. Women can receive a whole-uterine transplant and then give birth to healthy babies [1,2]. Grandmothers have gestated their own grandchildren using eggs donated from their daughters and sperm from their sons-in-law [3]. People with 'Swyer syndrome' (46,XY Sry mutation) have given birth with a donated egg after being induced to undergo puberty [4]. Beyond issues of infertility, assisted reproductive technology enables more LGBTQ+ couples to produce a genetically related child: e.g., gay men can donate sperm to a gestational surrogate, and lesbian couples can opt for "shared motherhood," by which one mother donates the egg and the other gestates the baby. Assisted reproductive technologies make possible what was once the realm of science fiction.

One might suspect that evolution could not possibly prepare a female body to gestate a fetus to which she is wholly unrelated. And yet, thanks to the power of egg donorship and assisted reproductive technology, more and more infants are born each year from donor eggs. The CDC reports that in 2021 in the USA, 4.4% of assisted reproductive embryo

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[1] Authors' note: Many people who make use of ART belong to the LGBTQ+ community. The authors note that, while the word "woman" is used in this article to describe pregnant people and those who produce ova, people of various gender identities could provide an ovum and/or gestate a pregnancy.

https://doi.org/10.1016/j.earlhumdev.2024.106072
Received 29 April 2024; Received in revised form 1 July 2024; Accepted 2 July 2024
Available online 2 July 2024

transfer cycles used gestational surrogacy, where someone else gestated the intended parents' embryo ($n = 8{,}862$ cycles). Further, 28,252 cycles used a donor egg or embryo while 217,835 used the patient's own egg/embryo [5]. However, we do not fully understand the physiological consequences of many reproductive technologies. When people use their own gametes to make a child with technological assistance, such as through in-vitro fertilization (IVF), the question is whether the procedures that are used to correct infertility are associated with other problems. Here, we focus on a special case that is interesting from an evolutionary perspective: when a woman gestates a wholly unrelated embryo through egg donation or gestational surrogacy. For gestational surrogacy to work, the maternal immune system must tolerate–and indeed, support–a totally foreign fetus.

To comprehensively discuss the spectrum of pregnancies that are now possible, we first must define our terminology (Box 1). In this paper, we use the term *gestational carrier* to refer to the body that is gestating the pregnancy, which may or may not be the intended mother, and may or may not be genetically related to the embryo. We use two terms to refer to pregnancies depending on how related the carrier is to the embryo: allogeneic (0% related) and semi-allogeneic (50% related, as in traditional pregnancies). *Allogeneic pregnancy* will refer to a pregnancy in which the ovum used to make the embryo originated in a different body from the body gestating the pregnancy; this could include a gestational surrogate or an intended mother using a donor egg. Relatedly, an *allogeneic embryo* refers to an embryo that is gestated in a different body from which it originated. *Semi-allogeneic pregnancy* refers to typical pregnancies, where the embryo is 50% related to the gestational carrier and 50% related to the sperm provider. That is, the ovum used to create the embryo is derived from the same body that gestates the pregnancy (what one might think of as a "natural" pregnancy). We note that some pregnancies are a special case where the embryo is somewhat–but <50%–related to its carrier, e.g., 25% if a genetic sister donates the egg. This is a middle ground between allogeneic and semi-allogeneic pregnancies (see Section 4).

Gestational surrogacy and pregnancy through egg donation are, by and large, the same biomedical phenomenon. In both cases, a gestational carrier gestates an allogeneic embryo (i.e., an embryo to which she is not related). Perhaps the largest difference is that gestational surrogates are typically healthier and more fertile than mothers who use traditional IVF with egg donation to bear a child. Surrogacy agencies and doctors screen potential surrogates to ensure they are healthy and have had at least one successful spontaneous pregnancy. In contrast, intended mothers using IVF with an egg donor likely face one or more problems with fertility, often due to advanced maternal age.

Before the recent advent of ovum donation, all human pregnancies were semi-allogeneic. In such pregnancies, the ovum-derived embryonic genome was identical by immediate genetic descent to a haploid set of genes present in the gestating body: embryos 'matched' gestating bodies with respect to ovum-derived genes but 'mismatched' gestating bodies with respect to sperm-derived genes. Conversely, gestating bodies also carried genes that 'matched' and 'mismatched' the embryo. Allogeneic pregnancies, in which there are an absence of matching genes, are an evolutionarily novel situation for which there can have been no prior specific adaptations. This absence of prior adaptations makes allogeneic pregnancies possible because such pregnancies are 'maladaptive' from the perspective of the genetic fitness of gestating bodies. However, the absence of partial matching is an immunologically and genetically novel situation in which mechanisms that are 'adaptive' in the context of semi-allogeneic pregnancies may malfunction. Semi-allogeneic pregnancy evolved as a complex interplay of evolutionary cooperation and conflict: cooperation because of the genes that were 'matched' between mother and fetus; conflicts because of genes that were 'mismatched' (Haig 1993, 1996). Therefore, aspects of intergenerational conflict are expected to be exacerbated in allogeneic pregnancies because of the absence of 'matching' genes.

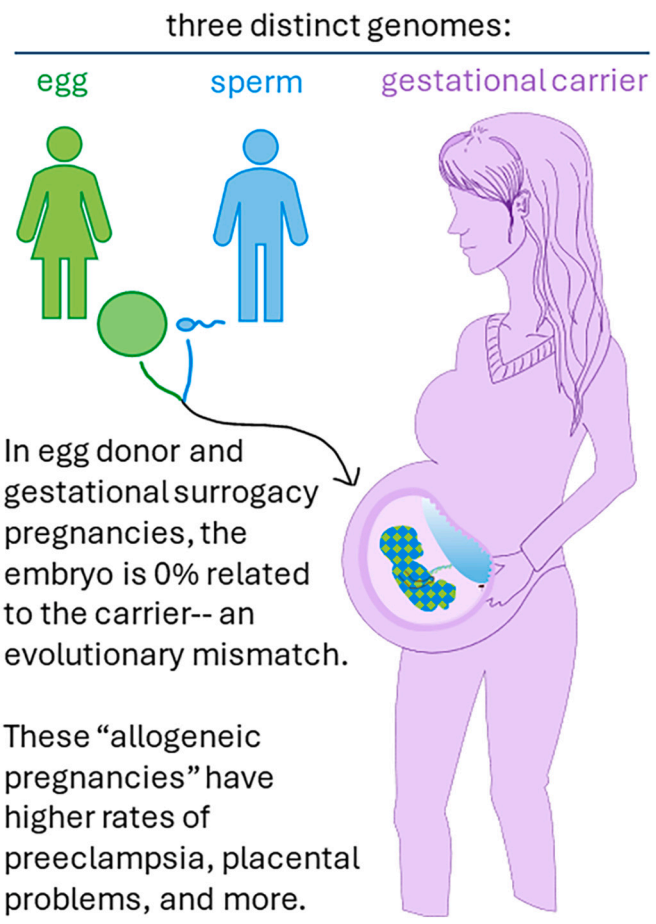

Fig. 1. Women gestating an unrelated embryo face a higher risk of preeclampsia and other conditions. Artwork modified from original work by Esther Fadumiye.

Further, all pregnancies result in maternal-fetal microchimerism,

Box 1
Glossary.

Gestational carrier: the body that is gestating the pregnancy; may or may not be the intended mother, and may or may not be genetically related to the embryo.

Allogeneic pregnancy: a pregnancy in which the embryo is unrelated to the gestational carrier, i.e., the ovum used to make the embryo originated in a different body from the body gestating the pregnancy Gestational surrogates or an intended mother using a donor egg.

Semi-allogeneic pregnancy: a traditional pregnancy in which the embryo is 50% related to the gestational carrier, i.e., a pregnancy in which the ovum used to create the embryo is derived from the same body that gestates the pregnancy.

wherein cells from the embryo pass into the maternal body and vice versa; these foreign cells persist in the body of both mother and child for many decades [6,7]. In traditional (semi-allogeneic) pregnancies, the microchimeric fetal cells found in mothers are 50% related to their mother's own genome; the same is true for the microchimeric maternal cells found in their children. But in allogeneic pregnancies, microchimeric cells do not match their primary genome at all. Do such wholly foreign microchimeric cells persist in the body of mother and child–or are they recognized as foreign and purged? For the cells that do persist, do they confer immunological challenges?

Intrafamilial egg donorship and gestational surrogacy can offer the opportunity to test a genetic "middle ground." Oftentimes, a sister agrees to participate in an allogeneic pregnancy to help her infertile sister become a mother. This can generally happen in one of two ways: either the fertile sister can donate the ovum for the infertile sister to gestate, or the fertile sister can gestate an embryo conceived with an ovum retrieved from the infertile sister. In these types of allogeneic pregnancies, the gestational carrier is 25% related to the embryo (rather than 50%, as in a semi-allogeneic pregnancy, or 0%, as in allogeneic pregnancies with a non-relative). Evolutionary theory predicts that sister-sister allogeneic pregnancies will have better maternal outcomes than those seen in unrelated allogeneic pregnancies.

As we review in the following text, medical research has documented the risks and outcomes of allogeneic pregnancies. However, to our knowledge, the current paper offers the first synthesis of the existing literature through the lens of evolutionary biology. Here, we evaluate how and why gestating an unrelated embryo carries extra risks above and beyond the risks inherent to assisted reproduction. In particular, we expect aspects of intergenerational maternal-fetal conflict to be exacerbated in allogeneic pregnancies. We review the available evidence on the maternal health challenges of pregnancies from gestational surrogacy and/or egg donation.

Consistent with evolutionary predictions, when a woman gestates a wholly unrelated embryo, she faces health challenges above and beyond those seen in traditional pregnancies conceived through in-vitro fertilization (IVF Fig. 1). This is true for infertile intended mothers receiving an egg donation (Section 2), where one might expect the egg to be healthy but the uterine environment to be suboptimal, and agency-screened gestational surrogates (Section 3), where one might expect the uterine environment to be healthy but the egg sub-optimal. Next, we hypothesize that unrelated embryos present a unique immune challenge to the carrier, complicating allogeneic pregnancies. As predicted by this hypothesis, risks seem to be lower when maternal-fetal relatedness is higher (Section 4): e.g., some evidence shows that sister-sister "allogeneic" pregnancies (25% relatedness) are lower-risk than unrelated allogeneic pregnancies (0% relatedness). Finally, we close by investigating what is known about microchimerism during allogeneic pregnancies (Section 5). While there is still little evidence available on microchimerism, we do know that fetal cells persist in maternal bodies for at least nine years after pregnancy with an unrelated allogeneic embryo [7]; we suggest that researchers consider long-term consequences of microchimerism in this novel reproductive reality.

Throughout this paper we focus on maternal health risks rather than infant health. Infants seem to face few health challenges from such pregnancies, except a small increased likelihood of low birth weight [8]. In cases where the mother develops preeclampsia, early birth can occur, and pregnancies with multiple embryos are riskier for the babies than singleton births. In general, beyond the specific issue of allogeneic pregnancy, babies born with the help of assisted reproductive technology face slightly increased risks of certain complications in the short and long-term, such as preterm birth and potential cardiometabolic diseases, although evidence is mixed (see Table 1 in [9]; see also [10] for a comparison of frozen and fresh embryo transfer).

2. Egg donorship: an intended mother gestates an unrelated embryo

2.1. Gestating an unrelated embryo causes health problems for the carrier above and beyond those typical of IVF

A collection of studies shows conclusively that gestating an unrelated embryo–an "allogeneic pregnancy"–is particularly risky for the carrier, above and beyond the normal levels of risk when undergoing IVF.

It is difficult to test whether allogeneic pregnancy is, itself, a risk factor because gestating a donated egg coincides with other potential risk factors such as advanced maternal age, multiple pregnancies (historically induced through IVF practices), and low fertility. Many studies of egg donorship are confounded by these features. But a carefully controlled matched-cohort study of healthy young women showed that allogeneic pregnancy from egg donorship is, itself, an independent risk factor for maternal and infant health [11]. In this study, researchers compared 259 women undergoing egg-donor-IVF/ICSI (intracytoplasmic sperm injection) with 515 undergoing IVF/ICSI with their own gametes. Embryos were transferred singly only, which removed the confounding risk of multiple births. All women were healthy and under the age of 40. Rodriguez-Wallberg and colleagues found that women who received a donated egg were four times more likely to develop hypertension disorders (adjusted odds ratio(AOR) = 4.25; 95% confidence interval (CI) = [2.61–6.92]), four times more likely to have preeclampsia (AOR = 3.99; 95% CI = [2.27–7.00]), more likely to require a cesarean section (AOR = 1.69; 95% CI = [1.22–2.35]), and more at risk for postpartum hemorrhage >1000 mL (AOR = 1.59; 95% CI = [1.11–2.27]) [11]. Overall, 44.7% of donor recipients experienced one or more pregnancy complications (compared to 30.6% of the control group). All risks were calculated in comparison to the control group, women undergoing IVF/ICSI with their own egg matched by age, IVF or ICSI, and year of transfer. In Rodriguez-Wallberg's study, all egg donors were unrelated to the intended parents and chose to donate eggs out of a sense of altruism.

Other well-controlled studies support the finding that receiving a donated egg is itself a risk factor above and beyond IVF. Evidence suggests that pregnancies using donated eggs also have a significantly higher incidence of postpartum hemorrhage [12]. Klatsky and colleagues found that allogeneic pregnancies resulting from egg donorship had a significantly higher risk of hypertension (n = 19.77, 24.7% vs n = 6/81, 7.4%, AOR = 4.2, 95% CI = [1.5–11.9]) and preeclampsia (n = 13/77, 16.9% vs n = 4/81, 4.9%, AOR = 4.0, 95% CI = [1.2–13.8]) compared to matched controls [13]. In another study, egg donor recipients were more likely to experience hypertension (n = 22/139, 16%) compared to matched control mothers undergoing IVF with their own eggs (n = 7/126, 5.5%) [14]; all pregnancies were single gestations. When Levron et al. bucketed health outcomes by (i) hypertensive disease or (ii) placental disease, controlling for maternal age, health, and other factors in a regression model, they found that egg donor recipients had higher odds of developing any hypertensive disease (AOR = 2.52; 95% CI = [1.18–5.35]) and any placental disease (AOR = 2.4; 95% CI = [1.22–4.78]) [14].

Further, the available meta-analyses support the conclusion that egg donorship increases the risk of pregnancy complications–particularly hypertensive diseases, and likely also postpartum hemorrhage and placental diseases [8,12,15–21]. In a large systemic meta-analysis, Storgaard and colleagues gathered 35 studies to evaluate the health outcomes of >16,000 egg donation pregnancies compared to >118,000 pregnancies conceived by IVF/ICSI and 1,000,000 spontaneously conceived pregnancies [21]. Singleton pregnancies with a donated egg faced a higher risk of hypertensive diseases, preeclampsia, low birthweight, preterm birth, and c-section than in IVF pregnancies with the mother's egg (AORs ranged from 1.55 to 3.31). Preeclampsia was the greatest risk of receiving a donated egg. After additional statistical analyses, the authors concluded that postpartum hemorrhage was also

more likely in mothers who received a donated egg compared to those undergoing IVF with their own egg. Interestingly, there was no increased risk of developing gestational diabetes and few small-for-gestational-age neonates.

A second large meta-analysis showed that pregnancies conceived with an egg donor were 4–5 times more likely to develop preeclampsia than natural conceptions and 2–3 times more likely than IVF conceptions with one's own egg ([16]; $n = 7089$ egg donation pregnancies, $n = 1,139,540$ natural conceptions, $n = 72,742$ IVF pregnancies; for egg donation versus natural conception, pooled OR = 5.09, 95% CI = [4.29–6.04]; for egg donation versus IVF, pooled OR = 2.97, 95% CI = [2.49–3.53]). Statistically, 5.9% of IVF users will develop preeclampsia, but egg donation likely increases the risk to 13.5% - 18.0%. Put another way, one in six women who use an egg donor will develop preeclampsia [16].

Additionally, placental complications (many immunological) are significantly more common in allogeneic pregnancies conceived through egg donorship [22]. The placenta is a fetally-derived organ that interfaces extremely closely with the maternal body. The authors state that placentae in allogeneic pregnancies show symptoms of a host-versus-graft rejection phenotype: T helper and natural killer cells were more abundant, as was trophoblast damage and fibroids with chronic deciduitis [22]. In another study, placentae from allogeneic egg donor pregnancies had significantly higher incidences of chronic villitis ($n = 12/36$ vs n = 1/55), chronic deciduitis ($n = 5/26$ vs n = 1/55), increased perivillous fibrin ($n = 10/36$ vs $n = 2/55$), infarction ($n = 11/36$ vs n = 2/55), and intervillous thrombi (n = 5/36 vs $n = 0/55$) – strong evidence of an immune-mediated response to an allogeneic embryo [23].

2.2. *Lesbian couples opting for shared motherhood may face higher odds of preeclampsia*

Keukens and colleagues [16] raise the case of shared motherhood in lesbian couples, by which one mother donates the egg and the other mother gestates the embryo; this situation allows both mothers to be biologically connected to their child. Through the phenomenon of microchimerism, the gestational carrier mother will swap cells with the fetus. These cells persist for many decades and have various phenotypic impacts ([7,24–26]; see Section 5 below). Even cells from an allogeneic fetus linger in the gestational carrier's body [7]. Thanks to microchimerism, the shared motherhood approach is indeed, physiologically, shared motherhood.

Based on what is known in allogeneic pregnancies generally (see previous sections), one would predict that preeclampsia and other complications will be higher in shared motherhood pregnancies. Lesbian couples likely do not have infertility issues, but recall that the risk of complications is higher with allogeneic pregnancies even in young, healthy, fertile, agency-screened gestational surrogates.

Indeed, in lesbian mothers who use the shared motherhood approach, the odds of preeclampsia are significantly higher for twin births, and non-significantly higher for singleton births (singletons: OR = 1.9, 95% CI = [0.7–5.2]; twins: OR = 21.7, 95% CI = [2.8–289.4]) [27]. In this study, Matorras and colleagues compared 660 IVF shared motherhood cycles to 4,349 typical sperm donor cycles (where the gestational carrier used her own egg with intra-uterine insemination), and controlled for maternal age [27]. The control and test group were not exactly the same, though, because one used IVF and one used intra-uterine insemination. While health outcomes for the gestational carriers were worse with the shared motherhood approach, studies of live birth outcomes indicate similar outcomes for babies from both the shared motherhood (allogeneic) and IVF/intrauterine insemination (semi-allogeneic) approaches [28]. Lesbian couples seeking shared motherhood typically undergo egg donation and allogeneic pregnancies for different reasons than infertile women. Mochtar and colleagues write that oocyte donation "should not be offered lightly to fertile, normal cycling women" [29]. In general, these studies provide data on risks and benefits for lesbian couples to consider as they choose how to conceive a child.

3. Gestational surrogacy: a healthy woman gestates an unrelated embryo for the intended parents

In the medical field, most studies and reviews of the health consequences of egg donorship compare mothers who received an egg donor with demographically-matched mothers undergoing IVF/ICSI (see Section 2). In this manner, doctors can isolate the health risks of egg donorship from the known health risks of (i) assisted reproductive technology itself (e.g., implanting an embryo) and (ii) maternal infertility and advanced maternal age. However, from an evolutionary perspective it is interesting to consider how healthy mothers who previously experienced uncomplicated childbirths would react to gestating an unrelated embryo. For this, we can turn to the literature on gestational surrogacy.

To become a gestational surrogate, women must typically fulfill a variety of conditions that demonstrate their health [30], including having had at least one successful and uncomplicated pregnancy. Many have written about how gestational surrogacy impacts infant health as well as the psychosocial lives of parents, children, and gestational carriers (see [31] for review). It is more difficult to determine the health risks for the gestational carrier, in part because the control group is not clear. A gestational carrier may wish to know how risky gestational surrogacy will be compared to her own previous traditional pregnancies. But in many cases, surrogate outcomes are compared to traditional IVF outcomes in subfertile intended parents. As you can see, these control groups are polar opposites: one is selected for maternal health and fertility (gestational carriers' prior births) and one is known to have below average fertility (intended parents undergoing assisted reproduction).

Surrogates commissioned to carry an unrelated embryo face higher health risks than they do in their own spontaneously conceived pregnancies (Sections 3.1, 3.2, 3.3, and 3.4). The medical literature does not always acknowledge the increased risks. For example, one clinical opinion paper found "no evidence of substantial adverse medical or psychological outcomes" for gestational carriers; but this compares carriers to intended mothers who undergo assisted reproduction themselves [30]. The claim of no adverse impacts for gestational carriers is flawed for two reasons. First, intended mothers undergoing assisted reproduction are not the appropriate control group for healthy surrogates. The intended mother is likely at risk of high complications, due to subfertility and/or advanced maternal age, whereas surrogates are screened for fertility and health. Second, evidence shows that gestational surrogates clearly experience a higher-risk pregnancy compared to their past, spontaneous, typically uncomplicated pregnancies: in surrogacy, (i) embryos are unrelated and (ii) IVF protocols are used, both of which independently confer additional risk.

If doctors tend to compare the risks of gestational surrogacy with the risks of assisted reproduction, they are not adequately informing potential surrogates of the increased risk *to themselves*. Further, many scholars have raised concerns about other aspects of informed consent for gestational surrogacy. In India from 2012 to 2013, before gestational surrogacy was banned, researchers found that 0 of 14 surrogates could explain the risks involved [32]. Writing in the North Carolina Journal of International Law, Pamela Laufer-Ukele points out that many gestational surrogates are pressured to waive informed consent or accede to demands from intended parents regarding medical procedures. For example, many surrogates sign contracts agreeing to a large list of medical procedures before they have met with doctors [33]. In general, only women who have had a successful pregnancy can be gestational surrogates because of "prolonged, intense, and unique nature" of pregnancy [34]. Following the same reasoning, we suggest that informed consent should include the understanding that the pregnancy is likely to be more complicated than the carrier's previous experiences.

3.1. Gestational surrogates of unrelated embryos face worse pregnancy complications across the board compared to spontaneous and traditional IVF pregnancies

Woo and colleagues compared gestational surrogate (allogeneic) pregnancies with traditional, spontaneous (semi-allogeneic) pregnancies conceived naturally by the same women who also served as surrogates [35]. They analyzed 249 spontaneous singleton pregnancies and 103 commissioned surrogate pregnancies in those 124 women, and found worse maternal outcomes across the board for surrogate pregnancies [35]. Gestational surrogate pregnancies had significantly higher rates of gestational diabetes (n = 7/103, 6.8% vs n = 3/249, 1.2%), hypertension (n = 7/103, 6.8% vs n = 7/249, 2.81%), use of amniocentesis (n = 7/103, 6.8% vs n = 0/249, 0%), placenta previa (n = 5/103, 4.9%, n = 3/249, 1.2%), antibiotic requirement during labor (n = 5/103, 6.2% vs n = 1/249, 0.5%), and c-sections (n = 19/103, 19.0% vs n = 18/249, 8.7%). Note that most of those c-sections appear to have been planned—possibly so that the intended parents could attend. Furthermore, mothers had a higher complication rate in surrogate pregnancies compared to spontaneous pregnancies for ten of eleven measured complications (the only exception being meconium complications). In the same study, the authors showed that surrogate births were more often preterm, lower birth weight, and lower mean gestational age at delivery [35]. It is interesting that amniocentesis was more common; perhaps parents using surrogates are more risk-averse.

3.2. Increased complication rates of surrogate pregnancy persist when healthy donor eggs and sperm are used; therefore, risks do not arise merely from "unhealthy" embryos

In Woo's study [35], the surrogates were gestating an embryo that originated from parents who could not, for one reason or another, gestate the embryo themselves. This raises a question: perhaps those embryos are sub-optimal, and it is the poor-quality embryo that creates a higher risk pregnancy. To control for this effect, Pavlovic and colleagues assessed health outcomes of surrogates for gay men or single intended fathers [36]. These surrogates received a donor egg from screened, healthy 21–28 year old egg donors and sperm from the healthy intended fathers [36]. For 66 surrogates, Pavlovic analyzed data on 78 commissioned surrogate pregnancies (allogeneic) and 71 spontaneous singleton pregnancies (semi-allogeneic). In other words, the authors compared the women's own traditional pregnancies with the pregnancies where they carried an unrelated embryo for the intended fathers. Commissioned surrogate pregnancies were 3.3 times more likely to include one or more complications even after controlling for the surrogate's age (n = 20/78 cycles, 25.6% vs n = 7/71 pregnancies, 9.9%). For example, 7 of 78 surrogate pregnancies (9%) had preeclampsia compared with 1 of 71 spontaneous pregnancies (1.1%). Gestational age at birth was also significantly lower in surrogate pregnancies. These results were significant after adjusting for age, since mothers are typically older when they serve as surrogates (having already had one or more spontaneous pregnancies is often a requirement for gestational surrogacy).

It is surprising that health challenges are worse in surrogate pregnancies, both because those women had undergone uncomplicated pregnancies before and because negative maternal health outcomes are typically lower in second (and beyond) births. However, allogeneic pregnancies seem riskier in general (see Section 2). Further, pregnancies tend to suffer more complications when women switch partners, possibly because prolonged exposure to a male's semen and sperm improves pregnancy outcomes [37–40]; surrogates usually have had no exposure to the genetic father's sperm and semen prior to gestating the pregnancy.

3.3. Certain very rare, dangerous complications of pregnancy are more frequent in surrogate pregnancies

Further, some ultra-rare and dangerous complications have been reported in a small series of surrogate pregnancies, such as hysterectomies due to major uterine damage. In a systemic review of 284 deliveries described in case reports and studies on obstetric outcomes from gestational surrogacy, Söderström-Antilla and colleagues confirmed that surrogate pregnancies are risky: 3.2–10% developed hypertensive disorders and 1.1–7.9% developed placenta previa/placental abruption [31]. Further, in three surrogate pregnancies, the surrogate had to have a hysterectomy due to critical complications: uterine atony, placenta accreta and uterine rupture [31]. Two of these three cases involved pregnancies with multiple embryos. These numbers were calculated based on 284 deliveries, 28 of which were actually traditional surrogacy where the carrier's own egg was used (i.e., semi-allogeneic). In these semi-allogeneic surrogacy cases, rates of complication were lower than in cases using an egg donor (allogeneic).

In 1% of surrogate pregnancies in the meta-analysis (3/284 studied; [31]), the surrogate underwent a peripartum hysterectomy–an extremely rare emergency treatment which has a general incidence of 0.0007% in high-income countries and 0.0011% globally [41]. In one case, the gestational carrier sustained a uterine rupture with no pre-existing uterine scar [42]–an event so rare it occurs in only one in 16,849 deliveries [43]. From these small sample sizes, we can tentatively conclude that surrogates are 900 to 1400 times more likely to require emergency hysterectomies than the average pregnant woman. Other data supports the starkly increased risk of hysterectomy from gestational surrogacy: in a controlled study comparing egg-donation pregnancies to traditional IVF, 3.8% of the egg donation pregnancies resulted in a postpartum hysterectomy (n = 3/79) compared to only 0.4% in traditional IVF (n = 1/234) [44]–a > 9-fold increase in risk.

3.4. Multiple embryo transfer–a major health risk to the carrier–is more common in surrogacy than in traditional IVF

In general, gestational carriers have more implantations, sustained pregnancies, and live births with a donor egg (allogeneic pregnancy) than do intended parents who gestate their own embryos (semi-allogeneic pregnancy) [45,46]. Since surrogates are screened for fertility and health, this is not surprising. Multiple embryo transfer is a primary known risk factor in any IVF-related assisted reproductive technology, including gestational surrogacy, and yet a recent review of surrogacy in the USA found that single embryo transfer was used in only 15% of cases [46]. Indeed, multiple embryo transfer was more common in surrogates than in intended parents undergoing IVF and pregnancy themselves [45]. Perhaps providers and intended parents decide to transfer more embryos to gestational carriers because surrogates are screened for health, and may therefore be considered better able to sustain complex pregnancies. A more cynical interpretation is that intended parents wish to get more "bang for their buck." Surrogacy is expensive. One might conclude that intended parents (and practitioners) are prepared to take greater risks with the body of the surrogate than with their own bodies.

4. Higher relatedness may reduce complications in allogeneic pregnancies

Evolutionary theory predicts that the maternal body will be more tolerant of a developing embryo that is genetically related to her. The maternal body may be less immunologically tolerant of a fetus that is 100% foreign rather than 50% foreign (semi-allogeneic). In the case of egg donorship pregnancies or surrogacy with a donated embryo, the gestational carrier is often unrelated to the embryo (allogeneic pregnancies). Indeed, allogeneic pregnancies cause more complications, such as preeclampsia and pathological placentation, which are attributed to immunological problems [8,22,23].

We may therefore predict that pregnancy will be more successful in cases where the allogeneic embryo happens to be a closer genetic or immunological match to the gestational carrier. Two lines of evidence support these evolutionary predictions: pregnancies seem to be less complicated when (i) a sister donates the egg rather than an unrelated individual, and (ii) the unrelated embryo happens to share more HLA types with their gestational carrier. That sister egg donations cause fewer complications is particularly strong evidence for the power of relatedness, given that sisters may be less healthy than agency-recruited egg donors (due to age, health status, and perhaps even sharing genetic traits with a subfertile sister).

Generally, if further research supports the idea that higher relatedness between carrier and embryo improves pregnancy outcomes, this opens interesting new avenues for egg donorship and gestational surrogacy screening programs. Perhaps intended parents could be matched with potential donors/surrogates based on genotyping and predictions of immunological compatibility, much the same way that kidney donors are screened for compatibility [81–84]. A market design mimicking kidney markets could also expand the pool of potential donors and surrogates.

Immunological response is not the only factor which may increase the risks of an egg donation pregnancy. Versen-Höynck and Griesinger [47] argue that egg donation pregnancies are riskier because the corpus luteum is absent. The corpus luteum is a temporary organ that develops on the ovary after ovulation, producing progesterone and other hormones required for a healthy pregnancy until the placenta has grown enough to take on that responsibility. In the programmed (i.e., artificial or hormone replacement therapy) cycles used in egg donation, the gestational carrier does not ovulate and therefore does not develop a corpus luteum in early pregnancy. Ovulation is suppressed so that embryo transfer can be aligned with the time when donor oocytes become available as well as to comply with the logistical/organizational needs of IVF clinics. The absence of a corpus luteum may well contribute to the increased risks of carrying an egg-donor pregnancy–an interesting idea worthy of further research.

4.1. Eggs donated by sisters may lead to fewer pregnancy complications than unrelated eggs

The first reported case of a familial gestational carrier was published in 1986, when a sister's egg was transferred into the intended mother's womb [48]. Shortly thereafter in 1988, the reverse occurred: the sister gestated an embryo made with the intended mother's egg [49]. Since then, many women have borne children using an egg donated from a sister, and many sisters have gestated an allogeneic donor embryo from their sister and brother-in-law. These cases present an opportunity to investigate the health consequences of gestating a more-allogeneic embryo (25% related)–less related to the carrier than the 50% of traditional pregnancy, but >0% related, as in the typical allogeneic pregnancy. Several studies hint at the result predicted by evolutionary theory: it is less risky to gestate a slightly-related embryo than a wholly-unrelated embryo.

Kim and colleagues showed that mothers receiving an egg from a sister had better pregnancy outcomes than those receiving from an unrelated donor [50]. Specifically, for 61 oocyte donation pregnancies compared to 127 traditional IVF pregnancies, the rates of pregnancy-induced hypertension were 20% among non-sister egg donors, 8% among sister egg donors, and 3.7% for standard IVF [50]. Non-sister egg donor pregnancies were significantly more likely to develop hypertension, with 6.5-fold greater risk ($p = 0.03$) than sister egg donor pregnancies. This study was reported as an abstract in a booklet of presentation abstracts, and the sample size for sister-donor pregnancies vs non-sister donor pregnancies was not reported.

In another study viewable only as an online abstract, Yang and colleagues [51] showed that early pregnancy loss and pregnancy-induced hypertension were "much higher" likelihood in carriers gestating an unrelated embryo versus an embryo where the egg was donated by a sibling. Gestational carriers with a non-sister donor lost the pregnancies early in 42.3% of cases ($n = 11/26$) compared to only 23.4% of traditional IVF pregnancies ($n = 32/137$). Gestational carriers with a non-sister donor experienced hypertension in 38.5% of pregnancies ($n = 5/13$), significantly more than the 8.8% of traditional IVF pregnancies ($n = 9/102$). The control group (traditional IVF) was matched to the oocyte donor group by age, parity, and multiple pregnancy. Apparently, data on hypertension and early pregnancy loss were not available for all pregnancies; overall the authors examined 37 oocyte donation pregnancies and 137 traditional IVF pregnancies. Some of the authors and dates overlap between [50,51]; it is therefore possible that the studied populations also overlap.

Two studies found that familial egg donors generally were no different from unrelated egg donors on a different set of outcomes, including ovarian responsiveness, birth weight, and live birth vs. miscarriage rate. Since these studies did not include hypertension and other maternal diseases of pregnancy, they are not directly comparable to Kim et al. [50] and Yang et al. [51]. Hasson et al. [52] found that ovarian and birth outcomes did not differ between pregnancies conceived with a family member's egg versus a stranger's egg ($n = 124$ from family members; $n = 306$ from unrelated donors). Outcomes were similar despite the fact that sister donors tended to be older, less responsive to ovarian stimulation, and with fewer ovarian reserves than non-sister donors. Similarly, Sung et al. found no difference in implantation and success rates between pregnancies with sister donors ($n = 13$) and non-sister donors ($n = 66$) to women with primary ovarian failure, but more cycles were canceled in sister-donor cases due to poor ovarian response [53]. Sung et al. [53] discuss the idea that sisters may be a poor choice for egg donors because they are genetically related to an infertile woman and may, therefore, have some traits that make pregnancy more difficult themselves.

In general, sister egg donors are likely less physiologically suitable candidates for egg donorship than young and healthy agency-screened egg donors. Therefore, it is surprising that sister-donor pregnancies have lower rates of complications [50,51] and no difference in implantation and birth outcomes [52,53]. Carriers who are more related to the embryo they gestate seem to fare better based on these small sample sizes.

4.2. Egg donor pregnancies may be more successful and uncomplicated with higher HLA matching between carrier and embryo

Evolutionary theory predicts that allogeneic embryos that seem less threatening (i.e., foreign) to a maternal immune system may result in more successful pregnancies. The human leukocyte antigen (HLA) gene complex is a highly diverse set of genes which play a major role in the immune system.

Lashley et al. (2015) showed that successful, uncomplicated pregnancies using an unrelated egg donor had a significantly higher-than-chance incidence of HLA matching between gestational mother and offspring [54]. The authors tested the HLA types HLAA, -B, -C, -DR, and -DQB for 75 mothers and their offspring conceived through successful egg donation. They found a significantly higher proportion of mother/offspring pairs with greater than or equal to five HLA matches (out of a possible 10) than expected (observed = 20, 26.7%; expected = 11, 14.7%) [54].

In a follow-up study, van Bentem and colleagues [55] showed that the development of preeclampsia in egg donor pregnancies was significantly associated with HLA class II mismatches between mother and fetus (OR = 3.8, 95% CI: 1.6–9.0; $p = 0.003$) [55]. The authors analyzed 76 singleton egg donor pregnancies, of which 13 developed preeclampsia. Mothers and neonates with more HLA class II mismatches were more likely to develop preeclampsia (odds ratio = 3.8, 95% CI = [1.6–9.0]; pregnancies with 2 HLA class II mismatches = 76.9%, $n = 10/13$, for preeclampsia pregnancies and 41.3%, $n = 26/63$ uncomplicated

pregnancies).

The story of immunological tolerance of pregnancy is, however, complicated [56]. The trophoblast has very low expression levels of classical HLA genes, presumed to be an adaptation to avoid immunological detection and destruction by the maternal body [57]. However, HLA matches play a role in later pregnancy and in the development of preeclampsia [56].

4.3. Further research is needed to determine whether dizygotic twins confer a greater immune stress than monozygotic twins

If we are considering the potential cost of genetic mismatch on the gestational carrier, one might predict that dizygotic twins, with two separate genomes, may confer a greater immunological challenge to the gestational carrier compared to monozygotic twins, even in traditional semi-allogeneic pregnancies. However, research finds mixed results, and zygosity itself is confounded by chorionicity—the number of placentae. Essentially all dizygotic twins are dichorionic (but see [58]), and essentially all monochorionic twins are monozygotic (though some monozygotic twins are dichorionic). Two placentae, rather than one, may be an independent risk factor. Some studies find that carriers of dichorionic or dizygotic twins have greater odds of developing pre-eclampsia/hypertension [59–62] and/or gestational diabetes [61,63]; for example, Sparks and colleagues found that preeclampsia developed in 21.1% (104/492) of dichorionic and 10.8% (22/203) of monochorionic pregnancies ($p = 0.001$; [59]). Others find no difference in preeclampsia rates between mono- and dizygotic, or mono- and dichorionic, pregnancies [64–66]; at least one study found that monochorionic or monozygotic pregnancies have higher odds of developing preeclampsia [67]. Confounding maternal factors may obscure the results [65], e.g., monozygotic twins are relatively more common in younger women, and monozygotic twins tend to deliver earlier. Both maternal age and fetal age-at-birth influence preeclampsia. Monochorionic twins are at risk of twin-twin transfusion syndrome, which may increase the risk of preeclampsia likely due to slowed growth rather than immunological challenge. Additionally, if there are fetal risk alleles for preeclampsia even at "non-immunological loci," mothers will be subject to increased exposure to these fetal alleles in dizygotic twins.

Further research is needed on twin zygosity and the immune challenge to the gestational carrier, particularly in the age of cheap genotyping. Studies could identify the risk of preeclampsia based on (i) whether twins are dizygotic, and (ii) how many total HLA-mismatches occur between the twins' genomes and the maternal genome.

By the same reasoning, we expect that triplet and higher-order pregnancies would have higher rates of preeclampsia in a dose-response manner according to the number of genomes present. Indeed, several studies show that the risk of preeclampsia and other diseases of pregnancy increases along a dose-response curve based on the number of embryos [68–71]. For example, when some triplet pregnancies achieved through IVF were reduced to twin pregnancies, the twin pregnancies had a lower rate of pre-eclampsia (15.8%, $n = 6/38$) than the matched unreduced triplet pregnancies (44.7%, $n = 17/38$) [69]. However, for higher-order pregnancies it is difficult to disentangle the specific effect of greater genetic mismatch from the general higher burden on a gestational carrier with each additional embryo.

5. Microchimerism may influence egg donor pregnancies and surrogates

Microchimerism in egg donor pregnancies is understudied and little understood [8]. In traditional semi-allogeneic pregnancies, cells derived from the fetus colonize maternal bodies where they can persist for many years, and cells derived from mothers can cross the placenta and similarly colonize fetal bodies [26]. These phenomena are known as fetal microchimerism (offspring cells in a mother's body) and maternal microchimerism (maternal cells in a child's body). These cells can persist for as long as we have measured them. In fact, pregnant women harbor microchimeric cells from their own mothers—"grandmaternal microchimerism"—which increase in frequency as the pregnancy goes on (by 12.7-fold from trimester to trimester [72]).

The microchimeric cell populations in maternal bodies have been implicated in health benefits for mothers (e.g., in tissue repair) and health problems for mothers (e.g., in some autoimmune diseases). Possible evolutionary implications of microchimerism have been considered in the context of the semi-allogeneic cells that our bodies have evolved with [24,25]. The implications of harboring allogeneic microchimeric fetal cells in the maternal body (and vice versa) for a sustained duration have not begun to be understood, but in this section we present potential outcomes based on what we do know.

5.1. Allogeneic cells from a wholly unrelated fetus can persist in a gestational carrier, through microchimerism, for at least nine years

One study has shown that cells derived from fetuses in allogeneic pregnancies can colonize maternal bodies and persist for at least nine years [7].

Williams et al. recruited 11 women who had conceived a male child using an egg donor, and they excluded any women who might carry male cells because of prior pregnancies, blood transfusions, organ transplants, or a male twin [7]. As a control population, they recruited eight women who used a donor egg to conceive a female child. Five of the 11 women who birthed males through egg donorship had cells with Y chromosomes present in their bloodstream, detected through the presence of the gene DYS14. None of the 8 women who birthed females through egg donorship showed the presence of Y chromosomes. Mean time since pregnancy was 56.0 months (SD 28.8) in the microchimeric group of mothers of males and 43.5 (SD 29.0) months in the non-microchimeric group of mothers of males.

But, to our knowledge, there have been no studies that inquire whether there are any health consequences from a body containing allogeneic microchimeric cells rather than semi-allogeneic cells. We suggest that researchers consider using animal models to investigate the health consequences of microchimerism in allogeneic pregnancies. For example, many studies of mice employ surrogate mothers to genetically modified embryos. What evidence of foreign allogeneic cells can be found in the gestating body and the newly-born mouse after the pregnancy? Do surrogate mothers, and pups born to surrogates, face immune challenges? Are microchimeric cells present at higher or lower frequency in a body when they are a total, rather than 50%, mismatch to the host genome?

5.2. Microchimerism may play a role in the health and disease of gestational carriers and children born from allogeneic pregnancies: what we can predict from indirect evidence

Microchimerism is implicated in the development of preeclampsia: mothers with preeclampsia have higher amounts of circulating fetal cells [72–74]. These studies tend to have small sample sizes but striking results. In 1988, Holzgreve and colleagues [73] showed that erythroblasts in maternal blood had significantly more fetally-derived cells in eight pre-eclamptic patients (9 cells per 1000, range 4–21) compared to eight uncomplicated pregnancies (2 cells per 1000, range 0–6). Decades later, in 2022, McCartney and colleagues [74] showed that immune cells in maternal blood from 16 preeclamptic patients had a significantly higher concentration of fetally-derived cells compared to 16 controls, measured using quantitative genetics and expressed in units of fetal genome equivalents per 10,000 maternal genome equivalents (gEq/10^5gEq) [74]. Specifically, they found significantly higher levels of fetally-derived B cells (mean concentration = 2 vs 74 gEq/10^5gEq) and Natural Killer NK cells (6 vs 20 gEq/10^5gEq). Concentrations of fetally-derived cells were also non-significantly higher for T cells, Tregs, and monocytes in pre-eclamptic mothers [74].

In general, very little is known about the fate and effects of microchimeric cells in both the gestational carrier and the child after an allogeneic pregnancy. However, gestational surrogates, recipients of egg donation, and children born through these processes should be followed for any evidence of immunological disease after a successful pregnancy. How numerous are microchimeric cells in such populations compared to traditionally reproducing populations? Among women with allogeneic pregnancies, are microchimeric cell counts correlated with the degree of HLA mismatch between egg donor and recipient?

6. Egg donors may experience health risks from donating eggs

Little is known about the risks of donating eggs. Egg donation is unusual in that young, healthy women undergo assisted reproductive procedures not to form their own offspring but to receive financial compensation (or for the sake of altruism). Often, researchers compare the health risks of oocyte donation to the health risks of undergoing IVF. However, are the two situations comparable? Someone may be more willing to undergo health risks for the sake of producing children than they would be for the sake of making several thousand dollars. Further, potential egg donors may wish to understand the health risks from donating eggs compared to opting out—not the health risks of donating eggs compared to the risks of IVF in an older and less fertile population of women. Nonetheless, the bulk of research compares the incidence of complications between oocyte donors and IVF participants. Researchers have found that egg donors typically are not aware enough of the medical and psychosocial risks of egg donation [75,76].

In one study, researchers looked at rates of minor and severe complications from 587 women who participated in 973 cycles and 886 egg retrievals [77]. Six patients (0.7%) experienced severe complications that required hospitalization, including ovarian hyperstimulation syndrome (OHSS), ovarian torsion, infection, and a ruptured ovarian cyst. As for minor complications, in 75 of 886 cycles (8.5%), the egg donor had a complication requiring at least one visit to the medical office, including 56 cases of mild or moderate OHSS, and in 36 cycles (4.2%) donors called the office to discuss symptoms of some kind that did not require a visit.

Two further studies showed that all cases of OHSS occurred when hCG was used as a triggering agent and none occurred when GnRH was used as the trigger. Bodri and colleagues researched 4,052 egg donation cycles from 1,917 donors, and found low complication rates: 22 donors experienced moderate to severe OHSS, 11 of which needed to be admitted to the hospital, and 17 patients experienced other complications, 14 of which required hospitalization and six of which required surgery [78]. The most common complication other than OHSS was intra-abdominal bleeding ($n = 14$). OHSS only occurred in patients where hCG was used as a triggering agent (0.87%) rather than a GnRH agonist. Similarly, Hernández and colleagues conducted a study of 429 IVF donor cycles, for which clinicians triggered ovulation with hCG in 175 cycles and a GnRH agonist in 254 cycles [79]. In the hCG cases, 3.2% of donors developed OHSS, of which 1% were severe. None of the GnRH patients developed OHSS.

The rates of complication reported in these studies are slightly lower for oocyte donors than for infertile women undergoing IVF. For example, the rate of OHSS is approximately 1% among infertile women undergoing IVF compared to 0.7% among oocyte donors (see discussion in [77]).

However, these rates of complication are substantially higher than the unknown, but low, rate of OHSS in natural pregnancies. The rate is not known because it is “very rare” with “only a few cases” reported in the literature [80]. Women who undergo egg donation may be more appropriately compared to (i) women conceiving naturally, without fertility challenges or (ii) women not attempting to become pregnant at all. When a patient considers an elective health procedure, they typically want to know the risks of complications relative to *their own* present and future if they choose not to have that procedure. Potential egg donors may be less interested in how their fate compares to a different population of people undergoing that procedure for different reasons.

7. Discussion

Remarkably, a woman can gestate a wholly unrelated embryo and give birth to a healthy baby. However, such “allogeneic” pregnancies are not without costs: the gestational carrier experiences significantly greater risks of preeclampsia, other hypertensive diseases of pregnancy, placental problems, hemorrhage, and more. Complication rates are higher even when the egg, sperm, and/or gestational carrier are known to be young and fertile. Risks are higher when the egg is healthy but the uterine environment may be sub-optimal, as with infertile intended mothers who use an egg donor (Section 2). Risks are also higher with a healthy uterine environment but a sub-optimal egg, as in agency-screened gestational surrogates (Section 3). Unrelated embryos seem to pose a special immune challenge to the gestational carrier (Section 4), a hypothesis borne out by some evidence that risks are lower in sister-sister allogeneic pregnancy, where the carrier is 25% related to the embryo rather than 0% related. Further research could clarify the role of relatedness. Microchimeric cells from an allogeneic embryo persist in the carrier’s circulation for at least nine years, raising interesting new research questions at a frontier of reproductive biology (Section 5). Finally, egg donors themselves likely face very low absolute risks but significantly heightened relative risks from undergoing the procedure (Section 6). Taken together, the predictions made by evolutionary theory can inform medical research and policy recommendations. We suggest three main areas where policy change or further research is needed.

First, who are the proper controls for assessing health risks of gestational surrogacy, egg donorship, and more? Often scientists use IVF patients, who will gestate their own embryo, as controls. But when fertile healthy women undergo these procedures for money or altruism, should we really be comparing their outcomes to infertile women undergoing these procedures in order to make a child? We propose that informed consent can only be obtained if these women understand the increased risk to themselves compared to (i) not undergoing the procedure or (ii) undergoing a typical semi-allogeneic pregnancy. Egg donorship and gestational surrogacy allow many intended parents to have children, a medical solution to deeply felt desire. By improving informed consent procedures, we can more smoothly pave the road to successful family planning.

Second, genetic relatedness may strongly affect pregnancy success, as in organ transplants. Indeed, sisters may be especially suitable egg donors and surrogates, contrary to some medical recommendations; doctors sometimes suggest that sisters may be sub-optimal because they may share genetic predispositions for infertility. We propose that a genetically related egg donor or gestational surrogate may be preferred, all else equal, based on the evidence outlined above about the risks of wholly-allogeneic pregnancies. Further, we highlight the need for research on HLA-matching and the odds of success in surrogate pregnancies. Initial evidence suggests that some sort of match scheme, similar to what is used for organ transplants [81–84], could improve pregnancy outcomes. A market and match system could also increase the total number of willing, and well-matched, donors and surrogates. More broadly, further research is needed on how important genetic relatedness is for maternal and infant health outcomes.

Third, regarding allogeneic pregnancies, little is known about microchimerism, sperm exposure (or lack thereof), and long-term health impacts. For example, we need to assess long-term health risks to children born of allogeneic pregnancies, the potential health outcomes of harboring fetal and maternal allogeneic microchimeric cells, and how the risks faced by a gestational carrier without sperm exposure compare to risks of a second birth in a spontaneous pregnancy with a new partner.

8. Conclusion

While modern medicine is able to support reproductive outcomes that have never before been encountered by the natural world, this novelty results in a biological mismatch which may result in unanticipated health consequences. Evolutionary history has not prepared our bodies to gestate wholly allogeneic embryos. It may be riskier than traditional pregnancies—but the real surprise is that we are capable of it at all.

CRediT authorship contribution statement

Dakota E. McCoy: Writing – review & editing, Writing – original draft, Conceptualization. **David Haig:** Writing – review & editing, Writing – original draft, Conceptualization. **Jennifer Kotler:** Writing – review & editing, Writing – original draft, Conceptualization.

Acknowledgements

DEM is supported by the Stanford Science Fellowship and the NSF Postdoctoral Research Fellowships in Biology PRFB Program, grant 2109465.

References

[1] M. Brännström, L. Johannesson, H. Bokström, N. Kvarnström, J. Mölne, P. Dahm-Kähler, et al., Livebirth after uterus transplantation, Lancet 385 (9968) (2015) 607–616. Feb 14.
[2] B. Jones, S. Saso, T. Bracewell-Milnes, M.Y. Thum, J. Nicopoullos, C. Diaz-Garcia, et al., Human uterine transplantation: a review of outcomes from the first 45 cases, BJOG 126 (11) (2019) 1310–1319.
[3] M.C. Michelow, J. Bernstein, M.J. Jacobson, J.L. McLoughlin, D. Rubenstein, A. I. Hacking, et al., Mother-daughter in vitro fertilization triplet surrogate pregnancy, J. In Vitro Fert. Embryo Transf. 5 (1) (1988) 31–34. Feb 1.
[4] J. Taneja, D. Ogutu, M. Ah-Moye, Rare successful pregnancy in a patient with Swyer syndrome, Case Rep Womens Health. 18 (12) (2016) 1–2. Oct.
[5] 2021 National ART Summary | CDC [Internet]. 2024 [cited 2024 Apr 9]. Available from: https://www.cdc.gov/art/reports/2021/summary.html.
[6] G.S. Dawe, X.W. Tan, Z.C. Xiao, Cell migration from baby to mother, Cell Adhes. Migr. 1 (1) (2007) 19–27.
[7] Z. Williams, D. Zepf, J. Longtine, R. Anchan, B. Broadman, S.A. Missmer, et al., Foreign fetal cells persist in the maternal circulation, Fertil. Steril. 91 (6) (2009) 2593–2595. Jun 1.
[8] M.L.P. van der Hoorn, E.E.L.O. Lashley, D.W. Bianchi, F.H.J. Claas, C.M. C. Schonkeren, S.A. Scherjon, Clinical and immunologic aspects of egg donation pregnancies: a systematic review, Hum. Reprod. Update 16 (6) (2010) 704–712. Nov 1.
[9] A. Pinborg, U.B. Wennerholm, C. Bergh, Long-term outcomes for children conceived by assisted reproductive technology, Fertil. Steril. 120 (3 Pt 1) (2023) 449–456. Sep.
[10] D. Galliano, N. Garrido, V. Serra-Serra, A. Pellicer, Difference in birth weight of consecutive sibling singletons is not found in oocyte donation when comparing fresh versus frozen embryo replacements, Fertil. Steril. 104 (6) (2015) 1411–1418. Dec. e1–3.
[11] K.A. Rodriguez-Wallberg, A.S. Berger, A. Fagerberg, J.I. Olofsson, C. Scherman-Pukk, P.G. Lindqvist, et al., Increased incidence of obstetric and perinatal complications in pregnancies achieved using donor oocytes and single embryo transfer in young and healthy women. A prospective hospital-based matched cohort study, Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 35 (4) (2019 Apr) 314–319.
[12] A. Shah, M. Parisaei, J. Garner, Obstetric complications of donor egg conception pregnancies, J Obstet Gynecol India. 69 (5) (2019) 395–398. Oct 1.
[13] P.C. Klatsky, S.S. Delaney, A.B. Caughey, N.D. Tran, G.L. Schattman, Z. Rosenwaks, The role of embryonic origin in preeclampsia: a comparison of autologous in vitro fertilization and ovum donor pregnancies, Obstet. Gynecol. 116 (6) (2010) 1387. Dec.
[14] Y. Levron, M. Dviri, I. Segol, G.M. Yerushalmi, A. Hourvitz, R. Orvieto, et al., The 'immunologic theory' of preeclampsia revisited: a lesson from donor oocyte gestations, Am. J. Obstet. Gynecol. 211 (4) (2014) 383.e1–383.e5. Oct 1.
[15] D.H. Adams, R.A. Clark, M.J. Davies, S. de Lacey, A meta-analysis of neonatal health outcomes from oocyte donation, J. Dev. Orig. Health Dis. 7 (3) (2016) 257–272. Jun.
[16] A. Keukens, M. van Wely, C. van der Meulen, M.H. Mochtar, Pre-eclampsia in pregnancies resulting from oocyte donation, natural conception or IVF: a systematic review and meta-analysis, Hum Reprod Oxf Engl. 37 (3) (2022) 586–599. Mar 1.
[17] P. Masoudian, A. Nasr, J. de Nanassy, K. Fung-Kee-Fung, S.A. Bainbridge, D. El Demellawy, Oocyte donation pregnancies and the risk of preeclampsia or gestational hypertension: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 214 (3) (2016) 328–339. Mar.
[18] U. Pecks, N. Maass, J. Neulen, Oocyte donation: a risk factor for pregnancy-induced hypertension, Dtsch Ärztebl Int. 108 (3) (2011) 23–31. Jan.
[19] V.M. Savasi, L. Mandia, A. Laoreti, I. Cetin, Maternal and fetal outcomes in oocyte donation pregnancies, Hum. Reprod. Update 22 (5) (2016) 620–633. Sep 1.
[20] J.E. Schwarze, P. Borda, P. Vásquez, C. Ortega, S. Villa, J.A. Crosby, et al., Is the risk of preeclampsia higher in donor oocyte pregnancies? A systematic review and meta-analysis, JBRA Assist Reprod. 22 (1) (2018) 15–19.
[21] M. Storgaard, A. Loft, C. Bergh, U. Wennerholm, V. Söderström-Anttila, L. Romundstad, et al., Obstetric and neonatal complications in pregnancies conceived after oocyte donation: a systematic review and meta-analysis, BJOG 124 (4) (2017) 561–572.
[22] F. Gundogan, D.W. Bianchi, S.A. Scherjon, D.J. Roberts, Placental pathology in egg donor pregnancies, Fertil. Steril. 93 (2) (2010) 397–404. Feb.
[23] Perni SC, Predanik M, Cho JE, Baergen RN. Placental pathology and pregnancy outcomes in donor and non-donor oocyte in vitro fertilization pregnancies. 2005 Jan 1;33(1):27–32.
[24] A.M. Boddy, A. Fortunato, M. Wilson Sayres, A. Aktipis, Fetal microchimerism and maternal health: a review and evolutionary analysis of cooperation and conflict beyond the womb, BioEssays News Rev Mol Cell Dev Biol. 37 (10) (2015) 1106–1118. Oct.
[25] D. Haig, Does microchimerism mediate kin conflicts? Chimerism 5 (2) (2014) 53–55.
[26] J.M. Kinder, I.A. Stelzer, P.C. Arck, S.S. Way, Immunological implications of pregnancy-induced microchimerism, Nat. Rev. Immunol. 17 (8) (2017) 483–494. Aug.
[27] R. Matorras, S. Perez-Fernandez, A. Hubel, M. Ferrando, F. Quintana, A. Vendrell, et al., Perinatal outcomes in lesbian couples employing shared motherhood IVF compared with those performing artificial insemination with donor sperm, Hum Reprod Oxf Engl. 38 (5) (2023) 895–907. May 2.
[28] P. Brandão, N. Ceschin, F. Cruz, R. Sousa-Santos, S. Reis-Soares, J. Bellver, Similar reproductive outcomes between lesbian-shared IVF (ROPA) and IVF with autologous oocytes, J. Assist. Reprod. Genet. 39 (9) (2022) 2061–2067. Sep.
[29] M. Mochtar, M. van Wely, A. Keukens, Reply: what is the true preeclampsia risk in oocyte donation pregnancies?—lack of deconfounding may lead to risk overestimation, Hum. Reprod. 37 (7) (2022) 1693. Jul 1.
[30] A. Yau, R.L. Friedlander, A. Petrini, M.C. Holt, D.E. White, J. Shin, et al., Medical and mental health implications of gestational surrogacy, Am. J. Obstet. Gynecol. 225 (3) (2021) 264–269. Sep 1.
[31] V. Söderström-Anttila, U.B. Wennerholm, A. Loft, A. Pinborg, K. Aittomäki, L. B. Romundstad, et al., Surrogacy: outcomes for surrogate mothers, children and the resulting families-a systematic review, Hum. Reprod. Update 22 (2) (2016) 260–276.
[32] M. Tanderup, S. Reddy, T. Patel, B.B. Nielsen, Informed consent in medical decision-making in commercial gestational surrogacy: a mixed methods study in New Delhi, India. Acta Obstet Gynecol Scand. 94 (5) (2015) 465–472.
[33] P. Laufer-Ukeles, The Disembodied Womb: Pregnancy, Informed Consent and Surrogate Motherhood [Internet]. Rochester, NY [cited 2024 Jun 18]. Available from: https://papers.ssrn.com/abstract=3210683, 2018.
[34] Ethics Committee of the American Society for Reproductive Medicine, Consideration of the gestational carrier: an Ethics Committee opinion, Fertil. Steril. 110 (6) (2018) 1017–1021. Nov.
[35] I. Woo, R. Hindoyan, M. Landay, J. Ho, S.A. Ingles, L.K. McGinnis, et al., Perinatal outcomes after natural conception versus in vitro fertilization (IVF) in gestational surrogates: a model to evaluate IVF treatment versus maternal effects, Fertil. Steril. 108 (6) (2017) 993–998. Dec 1.
[36] Z. Pavlovic, K.C. Hammer, M. Raff, P. Patel, K.N. Kunze, B. Kaplan, et al., Comparison of perinatal outcomes between spontaneous vs. commissioned cycles in gestational carriers for single and same-sex male intended parents, J. Assist. Reprod. Genet. 37 (4) (2020) 953–962. Apr.
[37] E.M. Pohjonen, V. Söderström-Anttila, C. Bergh, A. Loft, Å. Magnusson, A. Pinborg, et al., Obstetric and perinatal risks after the use of donor sperm: A systematic review and meta-analysis, Eur. J. Obstet. Gynecol. Reprod. Biol. 274 (2022) 210–228. Jul.
[38] H.S. Klonoff-Cohen, D.A. Savitz, R.C. Cefalo, M.F. McCann, An epidemiologic study of contraception and preeclampsia, JAMA 262 (22) (1989) 3143–3147. Dec 8.
[39] J.X. Wang, A.M. Knottnerus, G. Schuit, R.J. Norman, A. Chan, G.A. Dekker, Surgically obtained sperm, and risk of gestational hypertension and pre-eclampsia, Lancet Lond Engl. 359 (9307) (2002) 673–674. Feb 23.
[40] P.Y. Robillard, T.C. Hulsey, J. Périanin, E. Janky, E.H. Miri, E. Papiernik, Association of pregnancy-induced hypertension with duration of sexual cohabitation before conception, Lancet Lond Engl. 344 (8928) (1994) 973–975. Oct 8.
[41] A.F. Kallianidis, D. Rijntjes, C. Brobbel, O.M. Dekkers, K.W.M. Bloemenkamp, T. van den Akker, Incidence, indications, risk factors, and outcomes of emergency peripartum hysterectomy worldwide: a systematic review and Meta-analysis, Obstet. Gynecol. 141 (1) (2023) 35. Jan.
[42] D.A. Duffy, J.C. Nulsen, D.B. Maier, L. Engmann, D. Schmidt, C.A. Benadiva, Obstetrical complications in gestational carrier pregnancies, Fertil. Steril. 83 (3) (2005) 749–754. Mar 1.
[43] D.A. Miller, T.M. Goodwin, R.B. Gherman, R.H. Paul, Intrapartum rupture of the unscarred uterus, Obstet. Gynecol. 89 (5 Pt 1) (1997) 671–673. May.
[44] J G, A R, P G, A S, M P. A comparison of maternal and neonatal outcomes of 79 ovum donation pregnancies compared to 234 autologous Ivf controls. J Gynecol Reprod Med. 2017 Feb 16;1(1):1–5.

[45] J. Kapfhamer, B. Van Voorhis, Gestational surrogacy: a call for safer practice, Fertil. Steril. 106 (2) (2016) 270–271. Aug 1.
[46] K.M. Perkins, S.L. Boulet, D.J. Jamieson, D.M. Kissin, Trends and outcomes of gestational surrogacy in the United States, Fertil. Steril. 106 (2) (2016) 435–442. e2. Aug 1.
[47] F. von Versen-Höynck, G. Griesinger, What is the true preeclampsia risk in oocyte donation pregnancies?-lack of deconfounding may lead to risk overestimation, Hum Reprod Oxf Engl. 37 (7) (2022) 1692–1693. Jun 30.
[48] J. Leeton, L.K. Chan, A. Trounson, J. Harman, Pregnancy established in an infertile patient after transfer of an embryo fertilized in vitro where the oocyte was donated by the sister of the recipient, J. In Vitro Fert. Embryo Transf. 3 (6) (1986) 379–382. Dec.
[49] J. Leeton, C. King, J. Harman, Sister-sister in vitro fertilization surrogate pregnancy with donor sperm: the case for surrogate gestational pregnancy, J Vitro Fertil Embryo Transf IVF. 5 (5) (1988) 245–248. Oct.
[50] H.S. Kim, K.M. Yang, H.K. Ahn, C.W. Park, H. Kuol, I.S. Kang, et al., Obstetrical outcome after oocyte donation in patients with premature ovarian failure, Korean J Obstet Gynecol. 48 (1) (2005) 112–118. Jan 1.
[51] K.M. Yang, H.S. Kim, H.K. Ahn, C.W. Park, H. Kuol, I.S. Kang, et al., Obstetrical outcome after oocyte donation in patients with premature ovarian failure, Korean J Obstet Gynecol. 48 (1) (2005) 112–118. Jan 1.
[52] J. Hasson, T. Tulandi, W.Y. Son, N. al Ma'mari, A. Badeghiesh, S. Tannus, et al., Reproductive outcomes of familial oocyte donation, Fertil. Steril. 106 (7) (2016) 1696–1702. Dec 1.
[53] L. Sung, M. Bustillo, T. Mukherjee, G. Booth, A. Karstaedt, A.B. Copperman, Sisters of women with premature ovarian failure may not be ideal ovum donors, Fertil. Steril. 67 (5) (1997) 912–916. May.
[54] L.E.E.L.O. Lashley, G.W. Haasnoot, M. Spruyt-Gerritse, F.H.J. Claas, Selective advantage of HLA matching in successful uncomplicated oocyte donation pregnancies, J. Reprod. Immunol. 112 (2015) 29–33. Nov.
[55] K. van Bentem, M. Bos, C. van der Keur, S.H. Brand-Schaaf, G.W. Haasnoot, D. L. Roelen, et al., The development of preeclampsia in oocyte donation pregnancies is related to the number of fetal-maternal HLA class II mismatches, J. Reprod. Immunol. 1 (137) (2020) 103074. Feb.
[56] A. Martínez-Varea, B. Pellicer, A. Perales-Marín, A. Pellicer, Relationship between maternal immunological response during pregnancy and onset of preeclampsia, J Immunol Res 2014 (2014) 210241.
[57] A.L. Veenstra van Nieuwenhoven, M.J. Heineman, M.M. Faas, The immunology of successful pregnancy, Hum. Reprod. Update 9 (4) (2003) 347–357. Jul 1.
[58] G. Trombetta, D. Fabbro, E. Demori, L. Driul, G. Damante, S. Xodo, Rare spontaneous monochorionic dizygotic twins: a case report and a systematic review, BMC Pregnancy Childbirth 14 (22) (2022) 564. Jul.
[59] T.N. Sparks, Y.W. Cheng, N. Phan, A.B. Caughey, Does risk of preeclampsia differ by twin chorionicity? J. Matern. Fetal Neonatal Med. 26 (13) (2013) 1273–1277. Sep 1.
[60] Y. Wang, N. Wu, H. Shen, A review of research progress of pregnancy with twins with preeclampsia, Risk Manag Healthc Policy. 18 (14) (2021) 1999–2010. May.
[61] D. Maria, D.A. Manzoor, D.U. Ahmed, S. Aslam, H. Azhar, D.M.A. Haq, ul., Maternal-foetal conflict and genetic conditioning of intrauterine competition in sibling pairs: a systematic review, Ann Romanian Soc Cell Biol. 26 (01) (2022) 2025–2044. Jul 13.
[62] P. Bartnik, K. Kosinska-Kaczynska, J. Kacperczyk, W. Ananicz, A. Sierocińska, M. Wielgos, et al., Twin Chorionicity and the risk of hypertensive disorders: gestational hypertension and pre-eclampsia, Twin Res. Hum. Genet. 19 (4) (2016) 377–382. Aug.
[63] R.E. Hoskins, Zygosity as a risk factor for complications and outcomes of twin pregnancy, Acta Genet. Med. Gemellol. 44 (1) (1995) 11–23.
[64] M. Lučovnik, I. Blickstein, M. Lasič, V. Fabjan-Vodušek, G. Bržan-Simenc, I. Verdenik, et al., Hypertensive disorders during monozygotic and dizygotic twin gestations: a population-based study, Hypertens. Pregnancy 35 (4) (2016) 542–547. Oct 1.
[65] A. McFarlane, J.S. Scott, Pre-eclampsia/eclampsia in twin pregnancies, J. Med. Genet. 13 (3) (1976) 208–211. Jun.
[66] C.V. Maxwell, E. Lieberman, M. Norton, A. Cohen, E.W. Seely, A. Lee-Parritz, Relationship of twin zygosity and risk of preeclampsia, Am. J. Obstet. Gynecol. 185 (4) (2001) 819–821. Oct 1.
[67] D.M. Campbell, I. MacGillivray, Preeclampsia in twin pregnancies: incidence and outcome, Hypertens. Pregnancy 18 (3) (1999) 197–207.
[68] S.W. Wen, K. Demissie, Q. Yang, M.C. Walker, Maternal morbidity and obstetric complications in triplet pregnancies and quadruplet and higher-order multiple pregnancies, Am. J. Obstet. Gynecol. 191 (1) (2004) 254–258. Jul 1.
[69] D.W. Skupski, S. Nelson, A. Kowalik, M. Polaneczky, M. Smith-Levitin, J. M. Hutson, et al., Multiple gestations from in vitro fertilization: successful implantation alone is not associated with subsequent preeclampsia, Am. J. Obstet. Gynecol. 175 (4 Pt 1) (1996) 1029–1032. Oct.
[70] J.M. Mastrobattista, D.W. Skupski, M. Monga, J.D. Blanco, P. August, The rate of severe preeclampsia is increased in triplet as compared to twin gestations, Am. J. Perinatol. 4 (14) (2008) 263–265. Mar.
[71] S. Fiorentzis, S. Salta, M. Pargianas, A. Pontikaki, D.P. Koutsoulis, C. Akrivis, et al., Quadruplets and quintuplets, in: Multiple Pregnancy-New Challenges, IntechOpen, 2018.
[72] H.S. Gammill, T.M. Aydelotte, K.A. Guthrie, E.C. Nkwopara, J.L. Nelson, Cellular fetal Microchimerism in preeclampsia, Hypertension 62 (6) (2013) 1062–1067. Dec.
[73] W. Holzgreve, F. Ghezzi, E. Di Naro, D. Gänshirt, E. Maymon, S. Hahn, Disturbed Feto-maternal cell traffic in preeclampsia 1, Obstet. Gynecol. 91 (5) (1998) 669–672. Part 1. May 1.
[74] S.A. McCartney, T. Kolarova, S.B. Kanaan, A. Chae, C.I. Laughney, J.L. Nelson, et al., Increased fetal microchimerism in immune and stem cell subsets in preeclampsia, Am. J. Reprod. Immunol. 89 (3) (2023) e13666.
[75] E. Iranifard, S. Ebrahimzadeh Zagami, M. Amirian, H. Ebrahimipour, Roudsari R. Latifnejad, A systematic review of assisted and third-party reproduction guidelines regarding management and care of donors, Reprod. Health 21 (1) (2024) 75. Jun 1.
[76] P. Tulay, O. Atılan, Oocyte donors' awareness on donation procedure and risks: a call for developing guidelines for health tourism in oocyte donation programmes, J Turk Ger Gynecol Assoc. 20 (4) (2019) 236–242. Dec.
[77] K.N. Maxwell, I.N. Cholst, Z. Rosenwaks, The incidence of both serious and minor complications in young women undergoing oocyte donation, Fertil. Steril. 90 (6) (2008) 2165–2171. Dec.
[78] D. Bodri, J.J. Guillén, A. Polo, M. Trullenque, C. Esteve, O. Coll, Complications related to ovarian stimulation and oocyte retrieval in 4052 oocyte donor cycles, Reprod. Biomed. Online 17 (2) (2008) 237–243. Aug.
[79] E.R. Hernández, J.L. Gómez-Palomares, E. Ricciarelli, et al., Fertil. Steril. 91 (4, Supplement) (2009) 1358–1361. Apr 1.
[80] S. Sridev, S. Barathan, Case report on spontaneous ovarian hyperstimulation syndrome following natural conception associated with primary hypothyroidism, J Hum Reprod Sci. 6 (2) (2013) 158–161.
[81] A.E. Roth, T. Sönmez, M.U. Ünver, Efficient kidney exchange: coincidence of wants in markets with compatibility-based preferences, Am. Econ. Rev. 97 (3) (2007) 828–851.
[82] I. Ashlagi, A.E. Roth, Kidney exchange: An operations perspective, Manag. Sci. 67 (9) (2021) 5455–5478.
[83] A.E. Roth, T. Sönmez, M.U. Ünver, A kidney exchange clearinghouse in New England, Am. Econ. Rev. 95 (2) (2005) 376–380.
[84] S. Takemoto, F.K. Port, F.H.J. Claas, R.J. Duquesnoy, HLA matching for kidney transplantation, Hum. Immunol. 65 (12) (2004) 1489–1505.