Title: Uptake of invasive prenatal tests in pregnancies conceived via assisted reproductive technologies: the experience in Queensland, Australia.

Running Head: Uptake of invasive testing by women who conceived via ART

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What's already known about this topic?

- Prenatal diagnosis of chromosome abnormalities currently involves an invasive procedure, which has risk of fetal loss.
- Mixed results have been seen for the likelihood that women who have conceived via assisted reproductive technologies elect for invasive testing.

What does this study add?

- This study provides further evidence that pregnancies conceived using assisted reproductive technologies are significantly less likely to be subjected to invasive testing than pregnancies conceived spontaneously.
- Third largest cohort known to date.

Abstract

Objective: Prenatal diagnosis of a chromosomal abnormality currently involves the use of an invasive procedure, which has a risk of fetal loss. The aim of this study was to identify whether pregnancies conceived via assisted reproductive technologies were more or less likely to be subjected to an invasive procedure compared to pregnancies which were conceived spontaneously.

Method: Population data was collated from three private ultrasound clinics across south-east Queensland, Australia.

Results: Of the 15032 spontaneously conceived pregnancies, 775 (5.2%) had invasive testing. While 95 (6.0%) of the 1581 pregnancies conceived through assisted reproductive technologies had invasive testing. When the uptake of testing is adjusted by the maternal age the assisted reproductive population was significantly less likely to pursue invasive testing ($p=0.003$). Similarly when adjusted for the combined first-trimester screen risk estimate, the assisted reproduction population is significantly less likely to undergo invasive testing than the spontaneous population ($p=0.005$).

Conclusion: Pregnancies conceived using assisted reproductive technologies are significantly less likely to be subjected to invasive testing than pregnancies conceived spontaneously in women of the same age and cFTS risk.

Introduction

Diagnostic testing via an invasive procedure, such as Chorionic Villus Sampling (CVS) or Amniocentesis, is currently the only way a chromosomal abnormality can be confirmed prenatally. Both procedures are quoted (in Australasia) as having a miscarriage risk of approximately 1%¹. Due to the associated risk of miscarriage, these tests are only offered to women whose pregnancies are considered to be at high risk for aneuploidy. The combined first trimester screen (cFTS) is the most sensitive non-invasive clinical method of identifying a fetus as high risk for chromosomal abnormality². At the time of this study, a high risk (screen-positive) cFTS result indicated a risk between 1 in 2 and 1 in 300. The consequences of a screen-positive result include the offer of an invasive test, with risk of fetal loss due to the procedure, as well as psychological distress. With the cFTS there is an expected screen-positive rate of 5%, which means that 1 in 20 pregnancies screened will be placed in the high risk category³.

Pregnancies conceived via assisted reproductive technologies (ART) are sometimes considered 'precious' due to related difficulty in conception^{4,5}. The rate of achieving a pregnancy from one assisted reproductive cycle is approximately 23%, and the live birth rate per assisted reproductive cycle is estimated to be 17%^{6,7}. Due to the modest success rate, many patients require multiple cycles before having a healthy baby, and some will never have a successful outcome⁸. The number of clinical pregnancies resulting from assisted conception in Australia and New Zealand has increased significantly in recent years. At present, 1-3% of infants born in all developed countries are conceived through ART^{9,10}. The types of assisted reproductive technologies that are included in this study are *in vitro* fertilisation (IVF),

intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI), gamete intrafallopian transfer (GIFT) and medications that stimulate ovulation.

We hypothesized that women carrying pregnancies conceived via ART would be less likely to proceed to a diagnostic test due to the ‘precious’ nature of these pregnancies and the risk of miscarriage associated with an invasive procedure. This study aimed to identify if there was a difference in the frequency of diagnostic testing between those who conceived spontaneously and those who conceived via ART.

Methodology

Data related to prenatal screening and diagnosis was collated from three private ultrasound clinics in south-east Queensland, Australia. All centres use a commercial database, Viewpoint, (General Electric Healthcare, Waukesha, United States of America) to generate risks for chromosomal abnormality after first trimester screening. The databases were searched to identify pregnancies that had had first trimester screening, to detail method of conception, risks generated through screening and uptake of invasive testing. Pregnancies with multiple fetuses were excluded due to the additional complications associated with risk assessment and prenatal diagnosis. Any fetuses identified with chromosomal anomalies were removed from the data set as other risk factors may have been identified on ultrasound which could have affected the decision to test.

The data were analysed using Predictive Analytics Software Statistics (PASW) GradPack 17.0, part of Statistical Package for the Social Sciences (SPSS) Incorporated (Chicago, United States of America). The findings were considered significant when the p value was less than 0.05 ($p < 0.05$). A chi-square test was used to compare the uptake of invasive tests in the ART and spontaneous conception populations. Binary Logistic Regression analyses calculated the odds ratio (OR) that a pregnancy conceived through ART would have invasive testing, using the spontaneous conception population as a reference. The ORs were adjusted by two variables independently of each other. Both maternal age and the cFTS risk independently influence the decision to undergo an invasive test.

Ethics Approval

Approval was granted from the Griffith University Human Research Ethics Committee, protocol number BPS/01/09/HREC.

Results

17,889 women had combined first trimester screening at one of three centres between January 2004 and September 2009. 1157 multiple pregnancies and 119 fetuses with chromosomal anomalies were excluded. The final population of 16613 singleton fetuses included 1581 (9.5%) assisted conceptions.

Significant demographic difference when compared to spontaneous conceptions was an increase in maternal age (Table 1).

Table 1: Population demographics

870 (5.2%) women had an invasive prenatal test, 775 (5.2%) of those conceived spontaneously and 95 (6.0%) of those conceived through ART. Multivariate logistic regression that accounts for maternal age and the risk generated through combined first trimester screening shows that women who have had ART are significantly less likely to choose to proceed with an invasive test (Table 2, Figure 1).

Table 2: Analysis of uptake of an invasive test with Multivariate Logistic Regression

Figure 1

Discussion

On face value, invasive testing rates appear to be higher in the ART population (6.0% vs. 5.2%) but adjustment for maternal age and the risk generated through combined first trimester screening shows that women who have conceived through ART are significantly less likely to choose to proceed with invasive testing. This supports previous studies which found that the personalised risk from combined first trimester screening is the primary consideration in deciding upon invasive testing¹¹.

These findings support the hypothesis that women who have conceived through ART are less likely to proceed with a diagnostic test after combined first trimester screening. This is likely due to the clients heightened perception of the risk of miscarriage associated with an invasive procedure^{4,5}. It is unsurprising that the ART group would be more reluctant to risk miscarriage from an invasive procedure given this group's underlying difficulty with conceiving. In some cases the pregnancy is highly probably, the pregnant woman's only chance to have a child of her own and therefore particularly 'precious'⁵. Long-standing infertility or difficulty conceiving can evoke intense emotional responses⁴ and so consequently experiencing pregnancy loss could potentially lead to severe psychiatric responses¹². Hence, they may not be willing to take any additional risks, such as invasive testing during the pregnancy.

This study has the third largest cohort known to date. Amor *et al*¹³ in Victoria, Australia similarly found a higher proportion of women who conceived using ART (10.6%) had invasive testing compared to those who conceived spontaneously (5.3%). Amor *et al*¹³ had a population including 1793 women who conceived via ART. When maternal age was adjusted

for their results differed from ours, with the ART population 1.24 times more likely to undergo an invasive procedure. The maternal age and combined first trimester screen result were then simultaneously adjusted for and this showed the ART population was 0.78 times less likely to undergo invasive testing than the spontaneous population.

A Danish study of 8531 women who conceived via ART found that the invasive testing rate in this cohort was significantly lower than the general Danish population¹⁴. Meschede *et al*¹⁵ studied a group of 107 women who conceived via ICSI and found that this group was less willing to undergo an invasive procedure than women who had conceived spontaneously. Geipel *et al*¹⁶ confirms the hypothesis that women who conceived via ICSI favoured a non-invasive prenatal testing approach in a cohort of 153 women. Schover *et al*¹⁷ found in a sample of 55 couples that the risk of miscarriage associated with invasive testing strongly influenced the decision to undergo prenatal invasive testing. One study however, found no difference in the acceptance rate of invasive testing among women who conceived through ART compared with the general population¹⁸.

The data collated for this study was collected from three private ultrasound clinics and the population may therefore not reflect the general population seen in a public healthcare system. Most women undergoing assisted reproduction have private care in Queensland, given that IVF, IUI, ICSI, GIFT are not available in the Queensland public health care system. Therefore this contributes to the high prevalence of assisted reproductive conceptions in this cohort.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommend that all women, regardless of their age are offered the cFTS which may lead to an

offer of an invasive test³. All patients in this study received individual comprehensive counselling by either a genetic counsellor, fetal medicine specialist or specialised radiologist prior to any prenatal screening or invasive test. This counselling enables patients to understand the benefits, risks and limitations of both screening and invasive tests so an informed decision could be made. All the clinics reported that the vast majority of patients will undergo the cFTS initially and make decisions regarding an invasive test based on that result. Further analysis of this cohort found that the cFTS false-positive rate, when adjusted for maternal age was not significantly different between the assisted and spontaneously conceived populations¹⁹. There was one exception, the false positive rate was significantly increased ($p=0.012$) when conception included ICSI and the maternal blood serum was analysed by the KRYPTOR platform¹⁹.

ART pregnancies are not homogeneous – but it was not possible to examine subgroups due to the low numbers involved – which would have reduced the power of the study. It would be interesting to continue to investigate whether the type of treatment, number of cycles necessary to conceive and/or the reason for using ART had a direct relationship to the probability of pursuing invasive testing. Unfortunately some demographic variables such as education levels and parity were not examinable from the data extracted.

Women that have had ART are less likely to proceed to invasive testing after combined first trimester screening. This is consistent with our clinical impression of these being particularly ‘precious’ pregnancies and this study reminds us that risk alone does not dictate uptake of invasive testing. Rather, there are a myriad of factors which weigh into such decisions and it is our roles as clinicians to help the client identify and reconcile these factors so that they can make the best decision possible for them.

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Table 1: Population demographics

	Spontaneous	ART
<i>N</i>	15032	1581 (9.5%)
Maternal age (years)	32 (15-50)	34 (20-56) (p<0.001)
Maternal weight (kilograms)	64.5 (36-162)	65 (40-130)
Ethnicity	87% Caucasian	91% Caucasian
Smoking history	3% smokers	1% smokers

Table 2: Analysis of uptake of an invasive test with Multivariate Logistic Regression

	CVS or			Multivariate logistic regression analysis adjusting for:						
	Amniocentesis									
	<i>n</i>	<i>n</i>	%	Maternal Age			cFTS Risk			
				AdjOR	95% CI	p-value	AdjOR	95% CI	p-value	
All conceptions										
Spontaneous	15032	775	5.16	Reference			Reference			
ART	1581	95	6.01	0.701	0.55-0.89	0.003	0.718	0.57-0.91	0.005	

Figure 1:

The likelihood that spontaneously conceived pregnancies and pregnancies conceived via ART undergo an invasive procedure. The first pair of columns represents the odds ratio of the percentages calculated from the raw data. The second pair of columns represents the odds ratio when adjusted for maternal age. The third pair of columns represents the odds ratio when the combined first trimester screen risk is adjusted for. When the odds ratio is adjusted for maternal age or the combined first trimester screen risk, the likelihood that the ART population will undergo invasive testing is significantly reduced in comparison to the spontaneous conception population.