ETHICAL ISSUES IN RECRUITING PRENATALLY DIAGNOSED ADULTS FOR RESEARCH:

KLINEFELTER SYNDROME AS AN EXAMPLE

[SHORT COMMUNICATION]

Running title: Disclosing a prenatal diagnosis

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Since its introduction during the 1970’s, prenatal diagnosis has become more accessible and more accessed, with the number and range of genetic conditions able to be detected increasing as technology advances [1]. For many genetic conditions that can be identified by prenatal diagnostic testing, such as Down Syndrome (Trisomy 21), a clinical diagnosis would almost always be made at birth due to the obvious phenotype, if the condition was not identified prenatally. However, prenatal diagnosis, and even newborn testing, has opened the doors for the incidental identification of genetic conditions that may not be phenotypically explicit at birth, leading to a diagnosis earlier than one might expect should such testing not have occurred.

There are a number of ethical considerations that may arise around prenatal diagnosis and genetic information obtained about an individual prior to adulthood. Much of the current literature focuses on ethical issues confronting the couple or clinician during prenatal diagnostic testing, or around the rights and autonomy of children who may undergo genetic testing at an age where informed consent is not possible [2]. The purpose of this article is to highlight the more long-term ethical dilemmas that may arise around issues of disclosure regarding genetic information obtained prenatally or in the first few years of life, a topic that has not received much attention.

One example that raises substantial ethical issues arising from information obtained during prenatal diagnosis is Klinefelter syndrome (KS). KS is a common but under-diagnosed genetic condition, caused by an additional X chromosome in males (47,XXY). Symptoms range from azoospermia, small testes, testosterone deficiency and breast development, to varying degrees of learning, behavioural and cognitive difficulties, but can vary greatly between individuals [3]. Recent studies have estimated the prevalence of KS to be as high as 1 in 450 male births [4], and possibly increasing [5]. However, up to 70% of males are never diagnosed [6], because of low awareness of the condition amongst health professionals, the non-specificity of symptoms, and the reluctance of men to seek medical attention [7]. Many postnatal diagnoses occur in adulthood during fertility investigations, which may be beyond the point of optimal intervention [8].

Due to this lack of detection, many studies of KS suffer from ascertainment bias and small sample size, as research can only be carried out with the diagnosed population. A series of newborn screening surveys in the 1950’s and 1960’s provide the most comprehensive description of the natural history of the condition [9-13]. The conduct of newborn surveys for research purposes however, is generally no longer considered possible due to ethical considerations related to diagnosing children with conditions for which there is no direct
evidence of immediate benefit of diagnosis. Therefore, individuals diagnosed prenatally with KS, usually as an incidental finding during prenatal examination for advanced maternal age, provide a population of individuals for which it may still be possible to obtain follow up data free from diagnostic bias.

To conduct such follow up may depend on the ability to identify and contact individuals diagnosed prenatally and this raises important ethical considerations. We have experienced these recently in the process of conducting a study of adult men with KS. The initial study proposal aimed to recruit men diagnosed at different ages, including prenatally, in childhood, in adolescence and as adults. The prenatal group would act as a reference group for the other age at diagnosis groups. Adults now aged 18 years and older could only have been diagnosed prenatally between 1976 and 1991, and also considering potentially high termination rates for these pregnancies [14-15], it was anticipated that these numbers would be small. In fact, during this period in Victoria, only 35 cases of KS were diagnosed prenatally, and it is likely many of these pregnancies were terminated. For this reason, recruitment of the prenatal group would need to be more active than the other groups, who were being recruited via a range of sources: participants diagnosed with KS prenatally were to be identified and followed up from state and laboratory cytogenetic diagnostic data.

Further discussion of this recruitment highlighted a number of ethical issues. What if the parents of the prenatally diagnosed child had never informed the individual of their diagnosis? It could not be assumed that all parents would have told their sons about their diagnosis of KS, even if the sons had been receiving medical treatment or psychosocial interventions. Contacting the individual with KS directly thus ran the risk of disclosing information about them which they themselves did not know. In relation to any medical condition, this would be a shock [16], but in the case of a sex chromosome variation, it may be even more so. It would also have significant implications for the individual’s relationship with his parents, and the potential to cause serious rifts in the family.

This suggests that it would be ethically inappropriate to contact prenatally diagnosed individuals directly, even though they were now an adult. To circumvent this, but still allow this aspect of the study to be viable, it was speculated that potential participants would therefore have to be followed up through their mother, who could then choose whether or not to pass on study information to their adult child. Not only does this have a potentially negative impact on recruitment rate, it also raises questions about the researchers’ obligation or duty of care to the individuals with KS in this situation. If the son had not been told he had KS, does this prenatally diagnosed individual, now an adult, have a right to be told this
information – the ‘right to know’ in contrast to the ‘right not to know’ [17] – especially when testosterone treatment from puberty is recommended for up to 90% of patients, and could improve the quality of life of adults? [8]. In terms of respect for autonomy of the person with KS, and concern for their health and well-being, there seem to be strong ethical reasons to provide information about the diagnosis to men in this situation.

However, there are also ethical considerations against disclosure by the researchers. The damage that could be done has already been mentioned. It could also be seen as contravening the autonomy of the parents, and an invasion of the family’s privacy. Perhaps most important though, is the question of whether the researcher is the appropriate person to do the telling. There would be a strong argument that this should be done by a clinician, who has the interests of person with KS as the central consideration, and the capacity to assist medically and psychologically, rather than by a researcher whose main focus is on research, and who cannot provide on-going care and support. While many of these considerations are similar to those that arise in regards to cascade testing [18], disclosure in the case of prenatal diagnosis presents a unique situation. Ultimately, it was because of these ethical dilemmas that we decided to only utilise the recruitment strategy as designed for postnatally diagnosed individuals, emphasising specifically in the study information the need for those who had been diagnosed prenatally to take part.

These sorts of issues can also arise with other types of genetic information. Examples include information that is likely to have health implications that can be partially treated, such as sex chromosome variations; information with mild or untreatable health implications, such as use of in vitro fertilisation for conception of the individual, including donor sperm; information of unknown health consequences, such as mosaic karyotypes or apparently balanced de novo translocations; or information that will have later reproductive consequences, such as mutations of the cystic fibrosis gene resulting in congenital bilateral absence of the vas deferens in male carriers.

These questions have yet to be fully addressed by researchers, Human Research Ethics Committees, clinicians and the community. Yet they are important, and are not just theoretical speculations. Presumably, the majority of parents of a child prenatally diagnosed with a genetic condition would be alert for associated potential difficulties and access treatment if required. A child’s questions about treatment can often provide an opportunity for disclosure. However, it cannot be presumed that this is the case. Disclosure of these types of information from the parent to the child can be a difficult task, and currently there are few tools or resources to guide parents as to the how and when to disclose a diagnosis. The
A small number of our study participants diagnosed in childhood reported that they remember receiving medical attention whilst growing up, but a diagnosis of KS was not disclosed to them until they sought reproductive advice as adults. There is also evidence in relation to other medical conditions that parents do not always fully inform their children of conditions that are diagnosed in early childhood or prenatally [19]. In conditions like KS, where symptoms are non-specific, such individuals may remain in the dark well into adulthood. It is important to be able to conduct studies of this phenomenon, in order to assess the impact on individuals. Assuming that the impacts are negative, then further research is needed to design methods for assisting parents in telling their children, or to provide other avenues for passing on this information. What is needed now is ethical guidance on how to go about conducting such research.
References


