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Title: No evidence of adverse fertility and pregnancy outcomes in patients with unrecognised and untreated multiple endocrine neoplasia type 1

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Abstract

Objective

Literature concerning the impact of Multiple Endocrine Neoplasia Type 1 (MEN 1) on fertility is limited to case reports despite the early onset of endocrinopathies, such as primary hyperparathyroidism and prolactinoma, that may impact fertility. This study describes the impact of unrecognised and untreated MEN 1 on fertility and pregnancy outcomes in a multigenerational cohort of the Tasman 1 MEN 1 kindred.

Methods

All *MEN 1* positive (*MEN 1*$^{+}$, *n*=63) and *MEN 1* negative (*MEN 1*$^{-}$*, n*=75) descendants born between 1825 and 1951 of a common founder. Review of birth, death, marriage and medical records provided data on date of birth and death, gender, MEN 1 status and the number of pregnancies and children per parent.

Results

Compared to *MEN 1*$^{-}$ parents, *MEN 1*$^{+}$ parents had more children (RR 1.30, 1.02-1.66) and live births (RR 1.31, 1.02-1.67) with no excess of stillbirths (RR 1.24, 0.24-6.36). Compared to the era-matched Tasmanian fertility rate, *MEN 1*$^{+}$ parents had more children (4.87±4.11 *vs* 3.40±0.61, *p*=0.048), whereas *MEN 1*$^{-}$ parents had similar numbers of children (3.67±3.27 *vs* 3.36±0.62, *p*=0.55). *MEN 1*$^{+}$ parents had a similar number of *MEN 1*$^{+}$ and *MEN 1*$^{-}$ offspring (2.1±1.9 *vs* 2.5±2.3, *p*=0.31). Indirectly assessed miscarriage rate was similar between *MEN 1*$^{+}$ and *MEN 1*$^{-}$ mothers (*p*=0.77). Clinically overt pituitary disease reduced *MEN 1*$^{+}$ kindred member likelihood of parenthood (33% *vs* 97%).

Conclusions

There was no adverse impact of MEN 1 on patient fertility overall, however MEN 1-related pathology may have impaired the reproductive potential of a subset of individuals with pituitary disease.

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is a highly penetrant, autosomal dominant hereditary neoplasia syndrome caused by loss of function mutation in the *MEN 1* gene.[1-3] MEN 1 predisposes carriers to multi-system neoplasia including early-onset primary hyperparathyroidism, gastroenteropancreatic tumours, pituitary adenomas, particularly prolactinomas, adrenal, bronchial and thymic malignancy.[4-6] Primary hyperparathyroidism occurs in up to 75% of MEN 1 carriers before 21 years of age, requiring operative intervention in approximately one third.[7] Pituitary adenomas occur in up to one third of MEN 1 carriers before 21 years of age, with three quarters of affected patients women and 70% prolactinomas.[6, 7] Prolactinoma may reduce fertility[8, 9] and primary hyperparathyroidism is potentially associated with maternal and neonatal complications.[10, 11] Aggressive MEN 1-associated neoplasms may also occur at any age.[7]

Despite the early onset of MEN 1-associated manifestations that may impact reproductive health, data concerning the impact of MEN 1 on pregnancy and fertility is limited to isolated case reports and inference from experience with more common sporadic single organ dysfunction, such as isolated primary hyperparathyroidism.[12, 13] Directly translating experience from sporadic single organ dysfunction to patients with MEN 1 may not be appropriate as the pathophysiology, natural history and sequelae of MEN 1-related primary hyperparathyroidism and prolactinoma differs compared to sporadic counterparts.[6, 14-16] Existing case reports of MEN 1-associated pregnancies highlight challenging cases of MEN 1 during pregnancy,[12, 13] however these may be biased toward a complex

subset of MEN 1 patients. A comprehensive perspective on the impact of MEN 1 status on fertility is lacking.

Tasmania is an island state in Australia established as a European colony in the early 1800s with a small founding population, strong emphasis on record keeping and limited population migration. The early immigrant population of Tasmania included a founder carrying a pathogenic *MEN 1* genotype, the descendants of whom define the Tasman 1 MEN 1 kindred.[17,18] This pedigree spans from the 1825-present day and includes over 2500 individuals across nine generations. The MEN 1 population in Tasmania was first characterised in the mid-1980s, however the detailed record keeping in colonial Tasmania allowed tracing of the pedigree to the founding ancestors. Subsequent cross-referencing with historical birth, death, marriages and medical records provides the opportunity to understand the natural history and intrinsic impact of MEN 1 on fertility in a multigenerational MEN 1 cohort prior to the recognition of MEN 1 in Tasmania.

To determine the natural history of unrecognised MEN 1 on fertility and pregnancy outcomes we examined the effect of (1) parental MEN 1 status overall and (2) maternal and paternal MEN 1 status on reproductive outcomes.

Materials and methods

The Tasman 1 MEN 1 kindred contains over 2500 descendants of a common ancestor known to have carried a *MEN 1* NM_130799.2:c446-3, C.G gene mutation. Research undertaken since the 1980s has established the kindred pedigree by interrogating and cross referencing multiple historical records including births, deaths and marriages registries, medical and archival records and family surveys. All

contactable members of Tasman 1 MEN 1 kindred were invited to participate in a prospective MEN 1 screening program as previously described.[17,18] The medical records of those individuals dying before the commencement of prospective family screening were reviewed where available. The diagnosis of MEN 1 was based on 1) development of characteristic endocrine disease; 2) the presence of the Tasman 1 *MEN 1* gene mutation on genetic testing; or 3) a position in the pedigree mandating inheritance of the Tasman 1 *MEN 1* mutation. Kindred members who died prior to the availability of genetic testing were only designated as *MEN 1* positive (*MEN 1*$^{+}$) identified as obligate mutation carriers or if they developed of characteristic endocrinopathy that rendered the diagnosis highly probable on phenotypic criteria.[17,18] Data included date of birth (DOB), date of death, gender and MEN 1 status for parents and children. For parents, the number of pregnancies and children were also recorded. The research program was approved by the Human Research Ethics Committee of the University of Tasmania.

To establish the natural history and impact of MEN 1 on fertility only parents who completed their reproductive lifespan before the MEN 1 characterisation period in Tasmania were included. As the Tasman 1 MEN 1 kindred was first characterised in the mid-1980s with case identification extending into the 1990s, all descendents included in the present analysis were born prior to 1951. Thus the youngest descendent included in present analysis would have been 40 years of age by the time the Tasman 1 MEN 1 kindred was well defined in 1990.

To establish the impact of MEN 1 status on fertility all *MEN 1* positive (*MEN 1*$^{+}$) descendents were compared against all *MEN 1* negative (*MEN 1*$^{-}$) siblings within the Tasman 1 kindred. Data on miscarriage were not reliably available. Therefore, to indirectly assess the potential impact of MEN 1 status on miscarriage frequency, children were stratified by parental age at birth and the

proportions of children in each parent age category (<20, 20-25, 25-30, 30-35 and >35 years) compared. The hypothesis tested was that, if MEN 1 was associated with a significant increase in miscarriage rate, then on average births would be more likely to occur later in the reproductive lifespan. This would manifest as a higher proportion of births later in life to MEN 1 positive parents, particularly mothers.

To establish the impact of era of birth on fertility, *MEN 1*$^{+}$ and *MEN 1*$^{-}$ cohorts separated by median year of birth with the original Tasman 1 founder excluded as there was no contemporary *MEN 1*$^{-}$ siblings. To assess the generalisability of findings beyond the Tasman 1 kindred the number of children born to *MEN 1*$^{+}$ and *MEN 1*$^{-}$ parents within the kindred were compared with the average Tasmanian fertility rate adjusted by parental era of birth. Tasmanian total fertility rate was used to estimate the era-matched average Tasmanian fertility rate for all parents except those prior to 1886 where total fertility rates for Tasmania were unavailable and cohort fertility (children ever born) was used.[19-23] To establish the impact of 'parent of origin' (i.e. the parent who was *MEN 1*$^{+}$) on pregnancy outcomes all *MEN 1*$^{+}$ men were compared against all *MEN 1*$^{+}$ women.

Where data were not available for parent of origin MEN 1 status (*n*=1, 0.7%), child gender (*n*=9, 1.7%) or MEN 1 status (*n*=8, 1.5%), these data were excluded from the relevant analysis. Where disease or death likely impacted on the reproductive lifespan (defined as age 16-44 years; *n*=15, 10.8%), these data were included in initial analyses. As MEN 1 phenotype manifests in an age-dependent manner, for offspring MEN 1 status to be defined as positive or negative, the offspring had to live to at least 20 years of age or manifest clear MEN 1-related pathology prior to 20 years of age. Offspring who died prior to 20 years of age were classified as unknown MEN 1 status unless they had already developed unequivocal MEN 1-related pathology (*n*=1, 0.2%) prior to death.

Univariate analysis utilised t-tests and χ_2 tests to compare differences in means and proportions, respectively. Multivariable analysis utilised Log-Poisson regression analyses were used to investigate the relationship between parental MEN 1 status and number of births, live births, stillborn children, male and female children, paternal and maternal births. Negative binomial models were used to correct for over-dispersion where the assumptions of the Log-Poisson models were not satisfied. Data were transformed when not normally distributed. Statistical significance was defined as a two tailed p value ≤0.05. Data were collated and statistical analysis performed using GRAPHPAD PRISM (GRAPHPAD Software Inc. La Jolla, CA, USA) and R (The R Foundation, Vienna, Austria).

Results

Between 1825 and 1950 the Tasman 1 kindred comprised six generations and 137 descendants of a common ancestor. There were no births recorded after 1985 for members of the Tasman 1 kindred who were born prior to 1951.

Univariate analysis

Table 1 summarises cohort characteristics and fertility outcomes stratified by parental MEN1 status. 63 *MEN 1*$^+$ and 75 *MEN 1*$^-$ parents were included in the analysis, providing a 87% power to detect a 50% reduction in the number of pregnancies to MEN 1 parents taking the observed average number of births in the *MEN 1*$^-$ cohort and standard deviations in both groups. *MEN 1*$^+$ and *MEN 1*$^-$ parents were comparable with regard to median year of birth (1929 *vs* 1929, *p*=0.93) and gender balance (42.8 *vs* 56 % male, *p*=0.12). *MEN 1*$^+$ parents had more daughters (2.5±2.3 *vs* 1.7±1.8, *p*=0.02), but there was no significant difference between *MEN 1*$^+$ and *MEN 1*$^-$ parents with regard to the average number of children (4.9±4.1 *vs* 3.7±3.3, *p*=0.06), number of sons (2.3±2.3 *vs* 2.0±1.9, *p*=0.37) or proportion of stillborn children (1% *vs* 1.1%, *p*=0.75) in univariate analysis (Table 1).

There was no significant difference in the average number of children between *MEN 1*$^+$ and *MEN 1*$^-$ parent when stratified by median year (1929) of parent birth (Table 1). The proportion of children stratified by parental age at birth was similar between *MEN 1*$^+$ and *MEN 1*$^-$ parents as a whole (Table 1) and when only *MEN 1*$^+$ and *MEN 1*$^-$ mothers (χ_2 1.8, p=0.77) or fathers (χ_2 2.1, p=0.71) were considered. There was no significant difference between *MEN 1*$^+$ and *MEN 1*$^-$ parents as a whole (23.4±4.6 *vs* 23.4±4.0 years, p=0.88) or *MEN 1*$^+$ and *MEN 1*$^-$ mothers (21.6±3.3 *vs* 22.2±4.1 years, p=0.56) in the age at which they had their first child.

The proportion of descendents who reached reproductive age, but had events or pathology that interfered with reproductive lifespan (defined as 16-44 years of age) was similar between *MEN 1*$^+$ and *MEN 1*$^-$ kindred members (Table 1). The impact of interference with reproductive lifespan on number of births was similar between *MEN 1*$^+$ and *MEN 1*$^-$ kindred members ($p_{interaction}$=0.97). *MEN 1*$^-$ kindred members were more likely to have infectious disease, ischemic heart disease or accidental death as the cause for interference with their reproductive lifespan than *MEN 1*$^+$ kindred members (100% *vs* 11.1% of interference with reproductive lifespan, Table 2). There was a trend towards greater overall risk of death from accidental, infectious or cardiovascular aetiologies between 20 to 40 years of age in *MEN 1*$^-$ compared to *MEN 1*$^+$ kindred members (5 of 75 *MEN 1*$^-$ *vs* 0 of 63 *MEN 1*$^+$ kindred members). Two of three *MEN 1*$^+$ kindred members who reached reproductive age but had clinically overt pituitary disease did not have children compared to two of sixty *MEN 1*$^+$ kindred members who did not have clinically overt pituitary disease. The *MEN 1*$^+$ kindred member with clinically overt pituitary disease who had children first had their pituitary pathology become clinically overt after 55 years of age. A further *MEN 1*$^+$ kindred member died prior to reproductive age due to haemorrhage into a pituitary neoplasm.

Multivariable analysis

Table 3 summarises multivariate fertility outcomes of *MEN 1*$^{+}$ kindred members referenced against *MEN 1*$^{-}$ kindred members. Compared to *MEN 1*$^{-}$ parents, *MEN 1*$^{+}$ parents, particularly fathers, had a greater total number of children, live births and daughters parents in multivariable analysis. There was no difference between *MEN 1*$^{+}$ and *MEN 1*$^{-}$ parents with regard to the number of sons, maternal births or stillborn children (Table 3). After controlling for the total number of births, there was no significant deficit in the number of sons (RR 0.86, 0.67-1.10) or excess in the number of daughters (RR 1.12, 0.86-1.45) born to *MEN 1*$^{+}$ parents compared to *MEN 1*$^{-}$ parents.

To assess the external validity of these results, we compared *MEN 1*$^{+}$ and *MEN 1*$^{-}$ kindred members to the era-matched average Tasmanian fertility rate. There was no significant difference in the average number of children born to *MEN 1*$^{-}$ parents compared to the era-matched Tasmanian fertility rate (3.67±3.27 *vs* 3.36±0.62, p=0.55). *MEN 1*$^{+}$ parents had significantly more children compared to the era-matched Tasmanian fertility rate (4.87±4.11 *vs* 3.40±0.61, p=0.048). This was primarily driven by *MEN 1*$^{+}$ fathers (5.30±4.67 *vs* 3.30±0.54, p=0.04) rather than *MEN 1*$^{+}$ mothers (4.37±3.54 *vs* 3.42±0.48, p=0.40). Exclusion Tasman 1 kindred members whose reproductive lifespan was interrupted due to either premature death or significant pathology did not meaningfully alter the results of comparison between *MEN 1*$^{+}$ or *MEN 1*$^{-}$ parents and the Tasmanian fertility rate.

Table 4 summarises *MEN 1*$^{+}$ cohort characteristics and fertility outcomes stratified by parent gender. There was no significant difference between *MEN 1*$^{+}$ mothers and fathers with regard to parental year of birth, total number of births, sons or daughters, live births or stillbirths (Table 4). There was no significant difference in the average number of children per *MEN 1*$^{+}$ mother compared to *MEN 1*$^{+}$ father for parents who were born either before or after the median birth year (1929) for *MEN 1*$^{+}$

parents. The proportion of offspring after stratification for parental age was significantly different between *MEN 1*$^{+}$ mothers and fathers (p<0.001), with mothers having more children before 20 years of age (p=0.01) and fathers having more children after 35 years of age (p=0.04). Multivariable analysis adjusting for parental date of birth and interference with reproductive lifespan did not meaningfully change the results of univariate analysis (data not shown). There was no significant differences in the number of *MEN 1*$^{+}$ offspring compared to *MEN 1*$^{-}$ offspring from *MEN 1*$^{+}$ parents (2.1±1.9 *vs* 2.5±2.3, p=0.31) or the theoretical frequency of positive offspring for an autosomal dominant condition (p=0.23). The proportion of *MEN 1*$^{+}$ and *MEN 1*$^{-}$ children did not differ significantly with parental MEN 1 status (p=0.75).

Discussion

In this historical population-based analysis of the Tasman 1 MEN 1 kindred spanning six generations from 1825-1990 there was no adverse impact of MEN 1 on fertility, stillbirth rate or apparent miscarriage rate. Thus, despite encompassing a 165 year historical period during which MEN 1 was not recognised or treated and medical care only rudimentary during earlier generations, the reproductive success of *MEN 1* carriers was at least equivalent to sibling and population controls. While some instances of MEN 1-related pathology directly impairing reproductive potential were evident within the Tasman 1 kindred, *MEN 1* positivity did not appear to detrimentally impact fertility or *in utero* viability of the neonate for the majority of *MEN 1* carriers. Thus our data complement existing case reports, [12, 13] suggesting that for a subset of *MEN 1*$^{+}$ patients with high risk phenotypes, targeted intervention may be required. However, for the majority of MEN 1-related pregnancies, judicious investigation and a tendency towards careful antenatal observation may be a reasonable approach.

Strengths of this analysis include review of six generations spanning 165 years, strict case criteria to define *MEN 1*$^{+}$ status, restriction of the analysis to an era prior to MEN 1 being recognised in Tasmania and availability of *MEN 1*$^{-}$ sibling and contemporary population data to act as controls. To be designated as *MEN 1*$^{+}$, Tasman 1 kindred members had to manifest characteristic pathology, have a positive genetic test or occupy a position in the pedigree mandating inheritance of the *MEN 1* gene mutation. While all births for Tasman 1 kindred members born prior to 1951 were considered, there were no births to parents in this cohort after 1985. Thus all births considered in the present analysis occurred prior to 1985, a period when MEN 1 was unrecognised in Tasmania. The use of *MEN 1*$^{-}$ siblings as controls allowed tight matching of socioeconomic, geographic, lifestyle, era and non-MEN 1 genetic factors that may impact fertility. To confirm the external validity of this approach we used the era-matched fertility rate of the general Tasmanian population derived from census data. This demonstrated no difference between *MEN 1*$^{-}$ members of the Tasman 1 kindred and the broader Tasmanian population and produced similar findings whether *MEN 1*$^{+}$ parents were compared to their *MEN 1*$^{-}$ siblings or the era-matched population average. These findings support the generalisability of our findings and suggest that any potential misclassification of historical Tasman 1 kindred members with subclinical MEN 1 as *MEN 1*$^{-}$ did not meaningful impact results.

The total number of births and live births was greater for *MEN 1*$^{+}$ parents compared to *MEN 1*$^{-}$ siblings in multivariable analysis and population controls. It is theoretically conceivable that heterozygote loss of function of the *MEN 1* gene, as a bifunctional regulator of cell proliferation, may confer a reproductive advantage.[24, 25] However, the difference in births was attributable to paternal offspring and there was no increase in *MEN 1*$^{+}$ children. Based on these data it seems implausible that *MEN 1* positivity confers a biological reproductive advantage. The most likely explanation for this finding is survivor bias whereby for the Tasman 1 kindred to be recognised as a large MEN 1 pedigree, reproductive success, potentially in excess of the general population, in the preceding

generations was likely. Overall our data support the concept that MEN 1 does not adversely impact fertility for the majority of carriers, but that it is also unlikely to confer a biological reproductive advantage.

The equivalent fertility between *MEN 1*$^{+}$ and *MEN 1*$^{-}$ members of the Tasman 1 kindred suggests that the impact of MEN 1-related manifestations on fertility is not significant on a population basis. Primary hyperparathyroidism and pituitary adenomas, particularly prolactinomas, commonly occur before 20 years of age in MEN 1, though the majority are asymptomatic.[7] Primary hyperparathyroidism has traditionally been associated with a high frequency of maternal and neonatal adverse outcomes in case reports and series.[10, 11] However, more recent population based analyses suggest that the majority of patients with primary hyperparathyroidism can progress through pregnancy uneventfully and that the frequency of adverse outcomes appears to relate to the degree of hypercalcemia, rather than its presence or absence.[10, 26, 27] Our data support this perspective, as it is likely that the majority of maternal MEN 1 pregnancies would have occurred in the context of unrecognised primary hyperparathyroidism. However, examples of premature death secondary to complications of hypercalcemia within the kindred underline the need for judicious intervention.

Clinically overt pituitary neoplasms appeared to decrease the reproductive success of individual members in the Tasman 1 kindred, but subclinical pituitary disease, which is likely to have been present in a further 15-20%,[7] was not sufficient to impact on the fertility of the cohort as a whole. These data are similar to a limited analysis of a Finnish MEN 1 kindred, which lacked a comparator group, however described close to 100% reproductive fitness of *MEN 1*$^{+}$ members of the kindred.[28] Overall our data suggest that for the majority of MEN 1-associated pregnancies, judicious

investigation and a tendency towards careful antenatal observation may be a reasonable approach, but that for selected patients, targeted intervention may be required.

Directly assessed miscarriage rate was below the resolution of this historical cohort. To indirectly assess miscarriage rate, the proportion of births stratified by the parental age at which they occurred was compared. There was no significant difference in the proportion of births at each age category between *MEN 1*$^{+}$ and *MEN 1*$^{-}$ parents as a whole or when stratified by parental gender. This could be explained by (1) no significant increase in miscarriages associated with MEN 1 or (2) an increase in miscarriage rate in MEN 1 positive parents that is compensated for by an earlier entry into reproductive lifespan or higher fertility. Based on these results, researchers should expect to find either (1) no excess of miscarriages related to MEN 1, (2) an excess of miscarriages related to high risk phenotypes only that do not impact cohort fertility overall, or (3) or an excess of miscarriages that is balanced by greater number of total pregnancies. The absence of a significance difference in age at which MEN 1 positive parents had their first child suggests the third possibility is less likely.

There was no adverse impact of maternal *MEN 1*$^{+}$ status on reproductive success, offspring gender or offspring *MEN 1*$^{+}$ frequency. While *MEN 1*$^{+}$ mothers had children and completed their families earlier than *MEN 1*$^{+}$ fathers, there was no significant difference in the timing of children born to *MEN 1*$^{+}$ and *MEN 1*$^{-}$ mothers or *MEN 1*$^{+}$ and *MEN 1*$^{-}$ fathers, suggesting that non-MEN 1 factors were responsible. More daughters were born to *MEN 1*$^{+}$ parents, however this likely reflects the greater total number of births as adjustment for the total number of births in multivariable analysis rendered this result non significant. Importantly, there was no significant deficit in *MEN 1*$^{+}$ offspring compared to *MEN 1*$^{-}$ offspring or to the theoretical frequency of positive offspring for an autosomal

dominant condition and proportion of *MEN 1*$^{+}$ and *MEN 1*$^{-}$ children did not differ significantly with the parental MEN 1 status. This suggests that there is no disadvantage to neonatal MEN 1 *in utero* and that there is no major interaction between maternal and fetal MEN 1 status that detrimentally impacts survival to adulthood.

Misclassification of exposure or outcome is a common source of bias in population studies. Outcome measures (births and deaths) used herein were derived from historical databases, minimising the potential for outcome misclassification. Attributing *MEN 1*$^{+}$ status to MEN 1 phenocopy and *MEN 1*$^{-}$ status to undiagnosed subclinical MEN 1 both represent potential sources of bias secondary to misclassification of exposure in our analysis. Modern generations of the Tasman 1 MEN 1 kindred have had their MEN 1 status confirmed genetically, minimising the possibility of misclassification, however this was not possible for earlier deceased generations. MEN 1 phenocopy may account for up to 10% of cases of familial MEN 1 when sensitive diagnostic criteria such as isolated mild biochemical primary hyperparathyroidism or pituitary microadenoma together with family history are used.[29] However, misclassification of MEN 1 phenocopy as *MEN 1*$^{+}$ status is likely to be far less in the present analysis as earlier generations of were classified as *MEN 1*$^{+}$ only when unequivocal clinically overt MEN 1-related pathology manifested or if they were obligate carriers of the *MEN 1* gene mutation.

Strict case definition criteria may underestimate the prevalence of *MEN 1*$^{+}$ individuals. As MEN 1 phenotype manifests in an age-dependent, our criteria for *MEN 1*$^{+}$ status were particularly likely to result in misclassification if premature death from non MEN 1-related aetiologies intervenes. This is reflected greater interference with reproductive lifespan and a trend towards an apparent excess of early adulthood death from ischemic heart disease, infectious and accidental aetiologies in those

designated *MEN 1*$^{-}$ compared to *MEN 1*$^{+}$ kindred members in our cohort. Therefore the major source of misclassification error in our analysis is likely to be attributing *MEN 1*$^{-}$ status to subclinical MEN 1. To account for this we compared *MEN 1*$^{+}$ parents with non-sibling population averages. This yielded similar results to comparison with *MEN 1*$^{-}$ sibling controls, suggesting potential misclassification of siblings with undiagnosed subclinical MEN 1 as *MEN 1*$^{-}$ did not meaningfully impact results overall.

This analysis comprises a single large pedigree with a common *MEN 1* gene mutation, which may theoretically limit generalisability. However, to date there has been no reproducible genotype-phenotype relationship between the underlying MEN 1 gene mutation and clinical expression of disease.[5, 30-32] Genotypically heterogeneous cohorts have also demonstrated an age-related penetrance and spectrum of endocrinopathies comparable to the Tasman 1 kindred.[3, 5, 31, 33] For example, primary hyperparathyroidism is evident in approximately 67% of patients in the Tasman 1 kindred by 20 years of age and 75% of the genotypically heterogeneous Groupe d'étude des Tumeurs Endocrines (GTE) cohort by 21 years of age.[5,6, 7] Similarly the prevalence of prolactinoma at 20 years of age is 20% in the Tasman 1 kindred compared to 24% at 21 years of age in the GTE cohort.[6, 7, 33] Thus, while we cannot exclude the possibility that other *MEN 1* genotypes may differentially impact reproductive success, the lack of any reproducible genotype-phenotype relationship to date, comparable phenotypic expression and existence of other large MEN 1 kindreds in Finland,[34] Canada,[35] Belgium/France[4, 30] and the United States[36, 37] among others suggests our experience is not uncommon.

Our study had potential limitations. The impact of potential misclassification was minimised as described above. The impact of evaluating a single genotype on the generalisability of our findings has also been discussed. Our historical data demonstrate that the reproductive success of a subset of *MEN 1*$^{+}$ individuals may have been impacted by MEN 1-related pathology, however provided insufficient resolution to aid in predicting which individuals are particularly at risk. Similarly,

pregnancy complications that did not result in miscarriage or fetal demise were below the resolution of this historical database. Nonetheless, the absence of an era-dependent deficit in births suggests that the majority of MEN 1-associated pregnancies can proceed without events of sufficient magnitude to compromise the pregnancy.

In conclusion, there was no adverse impact of MEN 1 on patient fertility overall, however MEN 1-related pathology may have impaired the reproductive potential of a subset of individuals with pituitary disease. For the majority of MEN 1-related pregnancies, judicious investigation with a tendency towards careful antenatal observation appears to be a reasonable approach. Targeted intervention should be reserved for selected individuals with high risk phenotypes.

Declarations of interest: I certify that neither I nor my co-authors have a conflict of interest as described above that is relevant to the subject matter or materials included in this Work.

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Table 1. Cohort characteristics and fertility outcomes stratified by parental MEN1 status

	Parental MEN 1 status		
	MEN 1^{+} (*n*=63)	*MEN 1*$^{-}$ (*n*=75)	*p* value
Parental year of birth*	1929 (22.3)	1929 (24.5)	0.93
Parental gender (% fathers)	42.8	56.0	0.12
Average births (total)	4.9 (4.1)	3.7 (3.3)	0.06
Sons	2.3 (2.3)	2.0 (1.9)	0.37
Daughters	2.5 (2.3)	1.7 (1.8)	**0.02**
Live births	4.8 (4.1)	3.6 (3.3)	0.06
Stillborn children, % of total births	1.0	1.1	0.75

Paternal births	5.3 (4.7)	3.7 (3.3)	0.12
Maternal births	4.4 (3.5)	3.7 (3.3)	0.40
Average births per era			
Parent born ≤1929	6.32 (4.98)	4.21 (4.12)	0.07
Parent born >1929	3.22 (1.96)	3.08 (1.99)	0.76
Total births			
<20yoa	23	15	
20-25yoa	81	74	
25-30yoa	81	81	
30-35yoa	58	57	
>35yoa	46	38	0.78
Interference with reproductive lifespan† (%)	14.3	8	0.24

Boldface denotes statistically significant result.

Mean (SD), except for percentages. *p* values determined by t-test or $\chi 2$ tests as appropriate.

*Median year of birth and interquartile range

†Interference with reproductive lifespan was defined as death or significant pathology that was highly likely to have impacted fertility between 16-44 years.

Table 2. Events or pathology interfering with reproductive lifespan (16-44 years) stratified by MEN 1 status

Pathology or event	Number of kindred members	
	MEN 1^{+}	*MEN 1*$^{-}$
Clinically overt pituitary pathology	2	0
Death secondary to malignancy	5	0
Death secondary to complications of hypercalcemia	1	0
Death secondary to accident	1	2
Death secondary to ischemic heart disease	0	3
Death secondary to infection	0	1

Table 3. Multivariate fertility outcomes of *MEN 1*$^{+}$ kindred members referenced against *MEN 1*$^{-}$ kindred members

	Model 1†	Model 2‡
	RR (95% CI)	RR (95% CI)
Number of births	**1.28 (1.00-1.64)**	**1.30 (1.02-1.66)**
• Number of sons	1.14 (0.85-1.54)	1.16 (0.86-1.55)
• Number of daughters	**1.44 (1.07-1.93)**	**1.46 (1.09-1.95)**
• Number of paternal births	**1.42 (1.02-1.99)**	**1.45 (1.03-2.05)**
• Number of maternal births	1.16 (0.81-1.65)	1.14 (0.80-1.61)
Live births	**1.30 (1.01-1.66)**	**1.31 (1.02-1.67)**
Stillborn children	1.24 (0.24-6.36)	1.24 (0.24-6.36)

Boldface denotes statistically significant result.

†Model 1: adjusted for parental date of birth and gender.

‡Model 2: adjusted for parental date of birth, gender and interference with reproductive lifespan (16-44 years of age) due to death or significant pathology likely to interfere with reproductive potential.

Table 4. Pregnancy outcomes for *MEN 1*$^{+}$ parents stratified by parent gender

	MEN 1^{+} parent		*p* value
	Father (*n*=27)	Mother (*n*=35)	
Parental year of birth*	1928 (16.8)	1930 (25.5)	0.96
Average births (total)	5.3 (4.7)	4.4 (3.5)	0.40
Sons	2.3 (2.4)	2.2 (1.8)	0.80
Daughters	2.7 (1.9)	2.2 (2.2)	0.36
Live births	5.3 (4.7)	4.3 (3.5)	0.35
Stillborn children, % of total births	0.6	1.3	0.52
MEN 1^{+} births	2.2 (1.9)	1.9 (1.9)	0.56
MEN 1^{+} sons	19	28	
MEN 1^{+} daughters	38	35	0.21
MEN 1^{-} births	2.7 (2.6)	2.2 (2.1)	0.42
MEN 1^{-} sons	39	40	
MEN 1^{-} daughters	29	33	0.76

Average births per era			
Parent born ≤1929	7.54 (5.80)	5.38 (4.51)	0.28
Parent born >1929	3.21 (1.72)	3.53 (2.24)	0.65
Total births			
<20yoa	4	19	
20-25yoa	29	52	
25-30yoa	44	37	
30-35yoa	28	30	
>35yoa	33	13	**<0.001**

Boldface denotes statistically significant result.

Mean (SD), except for percentages. *p* values determined by t-test or $\chi 2$ tests as appropriate.

*Median year of birth and interquartile range