

English summary

Background

The use of fertility treatment is increasing worldwide. Fertility treatment circumvents natural conception by means of hormonal stimulation of the woman as well as chemical and mechanical manipulation of the gametes and the embryo. These interventions during the earliest stages of child development have raised concerns about potential adverse treatment effects. Previous research has shown an increased risk of adverse pregnancy outcomes in children conceived by fertility treatment, even in singleton births. However, studies investigating potential long-term health effects remain few.

The aim of this dissertation was to investigate the association between fertility treatment and somatic diseases in childhood.

Methods

A systematic review (study I) was conducted regarding assisted reproductive technology and somatic morbidity in childhood. Based on findings from this review, three birth cohort studies were designed (studies II–IV). Studies II–III investigated the association between fertility treatment and childhood epilepsy, addressing specific types of treatment and subtypes of epilepsy. Study IV investigated the association between specific types of fertility treatment and childhood type 1 diabetes mellitus.

Study II included all pregnancies resulting in live-born singletons from the Aarhus Birth Cohort, Denmark (1995–2013). Information on time to pregnancy and fertility treatment was obtained from pregnancy questionnaires. Studies III–IV included all pregnancies in Denmark resulting in live-born singletons (1995–2003), and information on fertility treatment was obtained from the Danish national health registers. In all three birth cohort studies (studies II–IV), children who developed epilepsy or type 1 diabetes mellitus were identified from the Danish national health registers until 2013.

Results

The systematic review (study I) included 38 published papers. The results indicated an association between assisted reproductive technology and infections and parasitic diseases, asthma,

genitourinary diseases, epilepsy or convulsions, and longer duration of hospitalizations. No association was seen between assisted reproductive technology and hospital admission, outpatient visits, or use of medication. Results were contradictory regarding mortality, cancer, pneumonia, allergy, and respiratory and gastrointestinal diseases.

The study on epilepsy in the Aarhus Birth Cohort (study II) included 60 440 pregnancies. Parental infertility or fertility treatment was not associated with childhood epilepsy but with the development of the subtype idiopathic generalized epilepsy.

The nationwide study on epilepsy (study III) included 565 166 pregnancies. Ovulation induction or intrauterine insemination was associated with a small increased risk of childhood epilepsy, and the association was related to clomiphene citrate treatment. The association was robust in a sibling analysis. In vitro fertilization or intracytoplasmic sperm injection was not associated with childhood epilepsy, but with a small increased risk of the subtype idiopathic generalized epilepsy.

The nationwide study on type 1 diabetes mellitus (study IV) included 565 166 pregnancies and showed no association between fertility treatment and the development of type 1 diabetes mellitus. However, ovulation induction or intrauterine insemination with follicle stimulating hormone was associated with the development of childhood type 1 diabetes mellitus.

Conclusions

The systematic review indicated an association between assisted reproductive technology and infections and parasitic diseases, asthma, genitourinary diseases, epilepsy or convulsions, and longer duration of hospitalizations.

The birth cohort studies on epilepsy showed that both parental infertility and fertility treatment were associated with an increased risk of the subtype idiopathic generalized epilepsy. Similar results were seen for in vitro fertilization or intracytoplasmic sperm injection. The associations with idiopathic generalized epilepsy may be due to characteristics of the infertile parents. Ovulation induction or intrauterine insemination with clomiphene citrate was associated with a small increased risk of childhood epilepsy. This risk may be due to a hormonal effect of clomiphene

citrate.

In the last birth cohort study, ovulation induction or intrauterine insemination with follicle stimulating hormone was associated with an increased risk of type 1 diabetes mellitus. This association may, however, be a chance finding or due to the characteristics of the infertile parents.

The studies in this dissertation add to the sparse knowledge regarding fertility treatment and somatic diseases in childhood.

Danish summary

Baggrund

Fertilitetsbehandling anvendes med stigende hyppighed over hele verden. Ved fertilitetsbehandling erstattes den naturlige befrugtning af både mekanisk og hormonel intervention. Dette har skabt bekymring for en eventuel skadelig effekt på børn der fødes efter disse behandlinger. Tidligere undersøgelser har vist, at børn undfanget ved hjælp af fertilitetsbehandling har en øget risiko for komplikationer under graviditeten, og at denne risiko formentlig ikke kun kan tilskrives den øgede forekomst af flerfoldsgraviditeter. Det er fortsat uafklaret, om børnenes helbred også er påvirket på længere sigt.

Formålet med denne ph.d.-afhandling var at undersøge associationen mellem fertilitetsbehandling og somatiske sygdomme i barnealderen.

Metode

Artikel I var en systematisk litteraturgennemgang vedrørende sammenhængen mellem assisteret reproduktionsteknologi og somatisk sygelighed i barnealderen. På baggrund af resultaterne i denne artikel designede vi tre fødselskohorteundersøgelser (artikel II–IV). I artikel II og III undersøgte vi associationen mellem fertilitetsbehandling og epilepsi i barndommen inklusiv specifikke behandlingstyper og subtyper af epilepsi. I artikel IV undersøgte vi associationen mellem specifikke typer af fertilitetsbehandling og type 1 diabetes mellitus i barnealderen.

I artikel II inkluderede vi alle graviditeter førende til enkeltfødte, levendefødte børn i den Aarhusianske fødselskohorte, Danmark (1995–2013). Information om ventetiden frem til graviditeten og fertilitetsbehandling blev indhentet fra spørgeskemaer udfyldt tidligt i graviditeten. I artikel III-IV inkluderede vi alle graviditeter resulterende i enkeltfødte, levendefødte børn i Danmark (1995–2003), og information om fertilitetsbehandling blev indhentet fra de danske nationale sundhedsregistre. I alle tre fødselskohorteundersøgelser (artikel II–IV) blev børn, der udviklede epilepsi eller type 1 diabetes mellitus indtil 2013 identificeret fra de danske nationale sundhedsregistre.

Resultater

Den systematiske litteraturgennemgang (artikel I) inkluderede 38 publicerede artikler. Resultaterne indikerede en association mellem assisteret reproduktionsteknologi og infektioner og parasitsygdomme, astma, urogenitalesygdomme, epilepsi eller kramper og længere gennemsnitlig indlæggelsestid. Der var ingen association med antallet af hospitalsindlæggelser, ambulante kontakter eller med medicinforbrug. Resultaterne var modstridende vedrørende mortalitet, cancer, pneumoni, allergi og respiratoriske og gastrointestinale sygdomme.

Undersøgelsen af epilepsi i den Aarhusianske fødselskohorte (artikel II) inkluderede 60 440 graviditeter. Forældrenes infertilitet eller fertilitetsbehandling var ikke associeret med epilepsi i barnealderen men med en øget risiko for subtypen idiopatisk generaliseret epilepsi.

Den nationale undersøgelse af epilepsi (artikel III) inkluderede 565 116 graviditeter. Ovulationsinduktion eller intrauterin insemination var associeret med en lille øget risiko for epilepsi, og associationen var relateret til behandling med clomifencitrat. Associationen var konsistent, når et søskendedesign blev anvendt. In vitro fertilisation eller intracytoplasmatisk sædcelleinjektion var ikke associeret med epilepsi i barnealderen men derimod med en lille øget risiko for subtypen idiopatisk generaliseret epilepsi.

Den nationale undersøgelse af type 1 diabetes mellitus (artikel IV) inkluderede 565 116 graviditeter. Fertilitetsbehandling var ikke associeret med type 1 diabetes mellitus i barnealderen. Derimod var ovulationsinduktion eller intrauterin insemination med follikelstimulerende hormon associeret med en øget risiko for type 1 diabetes mellitus.

Konklusioner

Oversigtsartiklen indikerede en association mellem assisteret reproduktionsteknologi og infektioner og parasitsygdomme, astma, urogenitalesygdomme, epilepsi eller kramper og længere gennemsnitlig indlæggelsestid.

Fødselskohorteundersøgelserne viste, at både forældrenes infertilitet og fertilitetsbehandling var associeret med en øget risiko for subtypen idiopatisk generaliseret epilepsi. Lignende resultater blev fundet for in vitro fertilisation eller intracytoplasmatisk sædcelleinjektion. Associationerne med idiopatisk generaliseret epilepsi kunne skyldes forhold hos de infertile forældre.

Ovulationsinduktion eller intrauterin insemination med clomifencitrat var associeret med en lille øget risiko for epilepsi i barnealderen måske pga. en hormoneffekt. Desuden var ovulationsinduktion eller intrauterin insemination med follikelstimulerende hormon associeret med type 1 diabetes mellitus i barnealderen. Dette resultat kunne dog være et tilfældigt fund eller skyldes forhold hos de infertile forældre.

Undersøgelserne i denne afhandling bidrager til den sparsomme viden om fertilitetsbehandling og somatiske sygdomme i barnealderen.