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Prospektive Evaluierung der vaskulären Morbidität von Nachkommen, die durch assistierte Reproduktionstechniken gezeugt wurden

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Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel

Prospektive Evaluierung der vaskulären Morbidität von Nachkommen, die durch assistierte Reproduktionstechniken gezeugt wurden

selbständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

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München, den 07.08.2025
Ort, Datum

Magdalena Silvia Langer
Unterschrift Magdalena Silvia Langer

Inhaltsverzeichnis

Abkürzungsverzeichnis

ART	assistierte Reproduktionstechniken / assisted reproductive technologies
PWV	Pulswellengeschwindigkeit / pulse wave velocity
cIMT	Intima-Media-Dicke der Karotiden / carotid intima-media thickness
IVF	In-vitro-Fertilisation / in vitro fertilization
ICSI	Intrazytoplasmatische Spermieninjektion / intracytoplasmic sperm injection
CVD	kardiovaskuläre Erkrankungen / cardiovascular diseases

Publikationsliste

In der folgenden Publikationsliste sind geteilte Erstautorenschaften mit einem * gekennzeichnet.

Originalarbeiten

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Posterpräsentationen

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Gender Disclaimer

In dieser Arbeit wird ausschließlich aus Gründen der besseren Lesbarkeit das generische Maskulinum verwendet. Die verwendeten Personenbezeichnungen beziehen sich – sofern nicht anders kenntlich gemacht – auf alle Geschlechter.

1. Beitrag zu den Veröffentlichungen

1.1 Beitrag zu Originalarbeit I

Mein Beitrag zur Originalarbeit „Vascular Health in Adults Born After Using Assisted Reproductive Technologies" fokussierte sich auf die Evaluation der vaskulären Morbidität von jungen Erwachsenen, die mittels assistierter Reproduktionstechniken (ART) gezeugt wurden. Dies umfasste zunächst die Datenerhebung. Nach der Akquirierung der ART- und spontan gezeugten Probanden, wurden diese zu einem drei- bis vierstündigen Studientag eingeladen, an dem eine ausführliche Untersuchung der kardiovaskulären Gesundheit vorgenommen wurde. Diese beinhaltete eine körperliche Untersuchung, anthropometrische Vermessungen, ein Ernährungsscreening, die Erhebung des ambulanten Blutdrucks, die Untersuchung mit dem EndoPAT™ 2000-Gerät, einen Sporttest, eine sonografischen Untersuchung der Karotiden und der abdominellen Aorta, eine Blutabnahme sowie die Anlage eines Blutdruckmessgeräts für eine 24-Stunden-Blutdruckmessung. Die Auswertung der EndoPAT™ 2000-Messungen beinhaltete die Inspektion der Grafiken und Übertragung der Messwerte in eine Excel-Tabelle. Diese wurde mit allen erhobenen Werten, insbesondere der ambulanten und 24-Stunden-Blutdruckwerte, der Pulswellengeschwindigkeit (PWV) und des laborchemischen kardiovaskulären Risikoprofils ergänzt. Die Intima-Media-Dicke der Karotiden (cIMT) wurde mittels eines Computerprogramms (QLAB Cardiovascular Ultrasound Quantification Software) jeweils einzeln analysiert. Im Anschluss habe ich die Daten statistisch mit SPSS ausgewertet und interpretiert. Die Anfertigung des Manuskripts, sowie die Überarbeitung und Ausarbeitung fiel ebenfalls in mein Aufgabengebiet. Im Prozess der Veröffentlichung war ich eng in den Revisionsprozess eingebunden.

1.2 Beitrag zu Originalarbeit II

Mein Anteil an der Originalarbeit „Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness" umfasste die Evaluation der arteriellen Steifigkeit in Nachkommen, die durch ART gezeugt wurden. Die Auswertung der sonografischen Bilder der Karotiden und der abdominalen Aorta mittels zweidimensionalem Speckle Tracking erforderte die manuelle Einstellung der *Region of Interest* mithilfe einer Software, die anschließend die gewünschten Parameter berechnete. Die weitere Datenerhebung erfolgte wie in Punkt 1.1 bereits beschrieben. In Zusammenarbeit mit meiner Co-Erstautorin wurden die Daten statistisch mit SPSS analysiert und interpretiert. Bei der Anfertigung des Manuskripts war vor allem die

Ausarbeitung und Überarbeitung der Einleitung, Methodik und Diskussion meine Aufgabe. Der Ergebnisteil wurde von meiner Co-Erstautorin übernommen. Der Revisionsprozess wurde von meiner Co-Erstautorin und mir gemeinsam betreut.

1.3 Weitere Beiträge

Im Rahmen des Promotionsvorhabens wurde ein weiterer Artikel in geteilter Erstautorenschaft sowie vier Artikel in Co-Autorenschaft veröffentlicht. Eine Übersichtsarbeit erschien in Co-Autorenschaft im Deutschen Ärzteblatt. Zudem habe ich vier Abstracts bei nationalen und internationalen Kongressen eingereicht und jeweils im Rahmen einer Posterpräsentation vor Ort vorgestellt. Bei sechs weiteren Abstracts war ich als Co-Autorin beteiligt. Weitere Details zu den Publikationen sind der Publikationsliste zu entnehmen.

2. Einleitung

2.1 Epidemiologie

Die Unterscheidung der Begriffe Sterilität und Infertilität ist weltweit wenig gebräuchlich (1). Dennoch ist eine Abgrenzung beider Begriffe von Bedeutung, da ihnen unterschiedliche Ursachen zugrunde liegen und daher in verschiedenen Therapieansätzen resultieren (1). Die Sterilität wird als das Ausbleiben einer Schwangerschaft innerhalb von zwölf Monaten ungeschützten Geschlechtsverkehrs definiert (2, 3). Infertilität beschreibt die absolute Zeugungsunfähigkeit, also das Unvermögen der Frau, eine Schwangerschaft bis zur Geburt eines lebensfähigen Kindes auszutragen, und Subfertilität die reduzierte Zeugungsfähigkeit (1, 2). Eins von sechs Paaren ist weltweit von einer Form der Zeugungsunfähigkeit betroffen (4). Die Ursachen hierfür liegen prozentual zu etwa gleichen Anteilen bei der Frau, dem Mann oder bei beiden (4). Etwa 50 % der betroffenen Paare nehmen ART als Maßnahme gegen ungewollte Kinderlosigkeit in Anspruch (5). Insgesamt liegen die Schätzungen der durch ART gezeugten Kinder weltweit bei über zehn Millionen (4). Länder wie Tschechien, Dänemark und Belgien verzeichnen mit etwa 4,0 % die höchsten Anteile an mittels ART gezeugten Kindern, während die USA mit etwa 1,0 % zu den Ländern mit den geringsten Anteilen zählen (4). In Deutschland liegt der Anteil bei etwa 3 % (6).

2.2 Definition der assistierten Reproduktionstechniken

ART spielen eine zentrale Rolle in der Kinderwunschbehandlung (1). Definiert sind ART als extrakorporale Maßnahmen, die mithilfe einer In-vitro-Behandlung von Oozyten, Spermien oder Embryonen auf die Initiierung einer Schwangerschaft abzielen (1, 3, 7). Zu diesen Maßnahmen zählen die In-vitro-Fertilisation (IVF), intrazytoplasmatische Spermieninjektion (ICSI), die Kryokonservierung von Gameten oder Embryonen sowie der Embryotransfer (1, 2, 3). Im Folgenden werden die IVF und die ICSI näher behandelt.

2.2.1 In-vitro-Fertilisation

Am 20. Juli 1978 wurde Louise Brown als weltweit erstes Kind mithilfe von IVF gezeugt (1). Dies stellte eine entscheidende Entwicklung in der Reproduktionsmedizin dar (1). Derzeit ist die IVF eine der am häufigsten verwendeten ART und umfasst im Allgemeinen die extrakorporale Befruchtung von Eizellen (4). Eine absolute Indikation zur IVF besteht bei tubarer Sterilität, wohingegen die idiopathische Sterilität nur eine relative Indikation darstellt (2). Zur Vorbereitung auf die IVF ist die kontrollierte ovarielle Stimulation der

Frau erforderlich (1). Mithilfe der Gabe von Gonadotropinen wird die Reifung einer möglichst hohen Anzahl reifer Follikel gewährleistet, sodass mehrere Embryonen zur Reimplantation in den Uterus zur Verfügung stehen und dadurch eine verbesserte Schwangerschaftsrate erreicht wird (1, 2, 8). Die Ovulation wird mittels einer Beta-hCG-Gabe ausgelöst (2). Nach ca. 36 Stunden folgt die transvaginale, ultraschallgesteuerte Follikelpunktion, bei der mithilfe Unterdruck die Eizellen mit den umgebenden Granulosazellen – auch Oozyten-Cumulus-Komplex genannt – aus dem Douglas-Raum gewonnen werden (2). Nach Trennung der Eizellen von den Granulosazellen werden diese inkubiert, nach Aufbereitung der Spermien des Partners mit diesen versetzt und erneut 16–18 Stunden inkubiert (1, 2). Der Embryotransfer in die Gebärmutterhöhle erfolgt im Vier-, Sechs- oder Achtzellstadium, etwa 48 Stunden nach Follikelpunktion (1, 2). Eine Schwangerschaftskontrolle erfolgt zwei Wochen nach der Follikelpunktion, und mit einer Wahrscheinlichkeit von etwa 20–24 % fällt diese positiv aus (1, 2). Die „Baby-take-home-Rate“, also die Erfolgsrate der lebend geborenen Kinder, pro Embryotransfer beträgt ca. 18 % (1). Bei Betrachtung der kumulierten Erfolgsrate, liegt diese nach bis zu vier Embryotransfers bei 50–60 % (1). Im Laufe der letzten Jahrzehnte wurden bedeutende methodische Fortschritte erzielt, wie etwa die Reglementierung der maximalen Anzahl an Embryotransfers sowie die optimierte kontrollierte ovarielle Stimulation (8). Diese Entwicklungen haben nicht nur die Qualität der Embryonen verbessert, sondern auch das Risiko von Behandlungskomplikationen verringert (8).

2.2.2 Intrazytoplasmatische Spermieninjektion

Über ein Jahrzehnt nach der Geburt von Louise Brown wurde die erste Schwangerschaft mittels ICSI erreicht (1, 9). Derzeit ist die ICSI die am häufigsten angewandte ART Europas und machte im Jahr 2017 ca. 70 % der ART-Behandlungen auf dem Kontinent aus (4). Grundsätzlich unterscheidet sich der Ablauf der ICSI erst nach der Follikelpunktion von dem der IVF (1, 2). Der Oozyten-Cumulus-Komplex wird mechanisch und enzymatisch aufgetrennt und die Eizellen werden auf Kernreife geprüft, die in der Metaphase II vorliegt (1, 2). In einer Petrischale werden die Spermien nach ihrer Aufbereitung und sorgfältiger Prüfung der Lage des Polkörpers in die Eizelle injiziert (2). Analog zur IVF, erfolgt eine Inkubation von 16–18 Stunden, bevor der Embryo in den Uterus zurückgebracht wird (1, 2). In den Erfolgsraten gibt es keinen Unterschied zwischen IVF und ICSI (1, 2, 4, 10). Die Entscheidung für die Verwendung der ICSI ergibt sich daher aus der Indikationsstellung: einer höhergradigen Subfertilität des Mannes, immunologisch bedingter Sterilität oder ungewöhnlich niedrigen Fertilitätsraten nach IVF bei unauffälligem Spermiogramm (1, 2, 10).

2.3 Morbidität von Nachkommen gezeugt mittels assistierter Reproduktionstechniken

Die steigende Zahl an ART-Nachkommen gibt Anlass, den Fokus auf mögliche kurz- und langfristige gesundheitliche Risiken zu legen (11). Im Folgenden wird zunächst die allgemeine kurz- und langfristige Morbidität von ART-Nachkommen behandelt. Darüber hinaus wird explizit auf die kardiovaskuläre Morbidität der ART-Nachkommen eingegangen.

2.3.1 Allgemeine Morbidität

Mehrlingsschwangerschaften stellen den größten nachteiligen Einfluss auf ART-Schwangerschaften dar (12). In Europa liegt der Anteil an Mehrlingsschwangerschaften nach einer ART-Behandlung bei ca. 15 % (4). Im Allgemeinen werden Mehrlingsschwangerschaften mit erhöhten Raten an Frühgeburtlichkeit, niedrigem Geburtsgewicht, erhöhter Neugeborenensterblichkeit und kongenitalen Malformationen assoziiert (12, 13). Bei ART-Mehrlingen ist das Risiko für Frühgeburtlichkeit und stark erniedrigtes Geburtsgewicht im Vergleich zu ART-Einlingen um das Fünffache erhöht (13). In der Literatur werden eine Reihe perinataler Risiken in ART-Nachkommen genannt: erhöhte Frühgeburtlichkeit, niedriges Geburtsgewicht, Small for Gestational Age, Totgeburten, erhöhte perinatale Mortalität sowie häufigere Notwendigkeit der Aufnahme auf eine neonatale Intensivstation (6, 7, 14, 15). Zudem treten angeborene Geburtsdefekte doppelt so häufig auf wie in spontan gezeugte Kontrollen (6, 7, 12, 16). Zu diesen Defekten zählen auch vermehrte Entwicklungsfehler während der Blastogenese, die zu Neuralrohrdefekten, Sirenomelie, Analatresie oder Amelie führen können (14). Genomisches Imprinting, die epigenetische Modifikation von Genen, ist beispielsweise bei der Entstehung des Angelman-Syndroms oder des Beckwith-Wiedemann-Syndroms beteiligt (15). Bei ART-Nachkommen mit diesen Syndromen wird das genomische Imprinting als Ursache dieser Erkrankungen häufiger beobachtet als bei spontan gezeugten Kontrollen (15). Im Vergleich zu den kurzfristigen gesundheitlichen Risiken sind die langfristigen gesundheitlichen Folgen von ART-Nachkommen in der Literatur weniger ausführlich erforscht (17). Neurologische Entwicklungs- und Verhaltensstörungen wie Zerebralparese, Epilepsie oder Aufmerksamkeits-/Hyperaktivitätsstörung treten vermehrt in ART-Kohorten auf (6, 12, 17, 18). Diese Zusammenhänge werden vor allem auf Frühgeburtlichkeit, Mehrlingsschwangerschaften und geringes Geburtsgewicht zurückgeführt (12, 17, 19). Das vermehrte Auftreten von respiratorischen Erkrankungen bei ART-Nachkommen im Vergleich zu spontan gezeugten Kontrollen wird mit der Subfertilität der Eltern in

Verbindung gebracht (17). Eine Vielzahl an Studien konnte keine statistisch signifikant erhöhte Prävalenz maligner Erkrankungen bei ART-Nachkommen im Vergleich zu spontan gezeugten Kontrollen feststellen (12, 15, 17, 20). Lediglich eine Assoziation von ART mit Rhabdomyosarkomen sowie Hepatoblastomen wurde gefunden (7, 12). Weitere Studien sind erforderlich, um die genauen Zusammenhänge zu klären (7, 12). Ein statistisch signifikant häufigeres Vorkommen von Erkrankungen des Zucker- und Fettstoffwechsels bei ART-Nachkommen konnte bislang nicht festgestellt werden (6, 7). Jedoch kann aufgrund eines statistisch signifikant erhöhten Nüchterninsulins bei ART-Kindern ein Trend zu einem beeinträchtigten Zuckerstoffwechsel im Vergleich zu spontan gezeugten Gleichaltrigen beobachtet werden (6). Angesichts der Tatsache, dass die Eltern der ART-Nachkommen bereits ART in Anspruch nehmen mussten, ist die reproduktive Gesundheit der Nachkommen von besonderem Interesse (15). Bei männlichen Nachkommen konnte eine verringerte Spermienzahl festgestellt werden, während bei weiblichen Nachkommen keine erhöhte reproduktive Morbidität beobachtet wurde (15, 17). Eine kanadische longitudinale Kohortenstudie untersuchte die Hospitalisierungsrate aufgrund von Infektionen, malignen oder allergischen Erkrankungen von 16.626 ART-Kindern im Vergleich zu 781.028 spontan gezeugten Kontrollen (21). Die ART-Kinder wiesen eine statistisch signifikant höhere Hospitalisierungsrate auf als die Kontrollkohorte (21). Nach Analyse der Geschwister und Adjustierung auf das mütterliche Alter konnte jedoch kein statistisch signifikanter Unterschied in den Hospitalisierungsraten zwischen den beiden Gruppen festgestellt werden (21).

2.3.2 Kardiovaskuläre Morbidität

In der Forschung herrscht Uneinigkeit über die kardiovaskuläre Morbidität von Kindern und Jugendlichen, die durch ART gezeugt wurden. Scherrer et al. untersuchten ausführlich die kardiovaskuläre Gesundheit von ART-Kindern (22, 23). Es wurden Hinweise auf vaskuläre Veränderungen gefunden, die auf eine vorzeitige Gefäßalterung hindeuten (22). Eine generalisierte endotheliale Dysfunktion konnte anhand der Messung der Flow-Mediated Vasodilatation der brachialen Arterie ermittelt werden. Die Flow-Mediated Vasodilatation war bei ART-Kindern etwa ein Viertel geringer als bei spontan konzipierten Kontrollen, was erste Hinweise auf eine mögliche vorzeitige Atherosklerose in dieser Gruppe liefert (22). Zudem konnte die endotheliale Dysfunktion auch im pulmonalen Gefäßsystem nachgewiesen werden (22, 23). Strukturelle Veränderungen und eine erhöhte arterielle Gefäßsteifigkeit äußerten sich in einer statistisch signifikant erhöhten cIMT sowie einer schnelleren PWV (22). Klinisch manifestiert sich diese vaskuläre Dysfunktion häufig zuerst in einem erhöhten arteriellen

Blutdruck (22). Eine Follow-up-Studie der Autoren bestätigte diese Ergebnisse auch bei Jugendlichen und jungen Erwachsenen (24). Die Evaluation von 225 IVF-Kindern und 225 spontan gezeugten Kontrollen ergab ebenfalls einen statistisch signifikant erhöhten systolischen und diastolischen Blutdruck bei IVF-Kindern (25). Die untersuchten IVF-Kinder befanden sich doppelt so häufig in den höchsten Quartilen des systolischen und diastolischen Blutdrucks (25). Die Studie von Zhang et al. konnte eine statistisch signifikant dickere cIMT und eine statistisch signifikant schnellere PWV bei IVF-Kindern im Vergleich zu spontan gezeugten Kontrollen nachweisen und stützt damit die Annahme einer erhöhten kardiovaskulären Morbidität in der ART-Kohorte (26). In einer Untersuchung von 382 ART-Kindern im Vergleich zu 382 spontan gezeugten Kindern wurden neben einem statistisch signifikant erhöhten arteriellen Blutdruck auch Veränderungen der linksventrikulären Struktur und Funktion festgestellt (27). Das kardiale Remodelling zeigte sich durch eine rechtsbetonte Veränderung der Herzmorphologie, ein dilatiertes Atrium oder verdickte Myokardwände (28). Diese Veränderungen scheinen postnatal fortzubestehen und haben Auswirkungen auf die kardiale Effizienz (22, 28).

Diesen Ergebnissen gegenüber stehen Studien, die eine erhöhte kardiovaskuläre Morbidität in ART-Nachkommen nicht stützen. Um potenzielle kardiovaskuläre Auswirkungen von ART auf Kinder zu untersuchen, analysierte die Studie von Huang et al. 83 ART-Nachkommen und 1.095 spontan gezeugte Kontrollen im Alter von sechs Jahren (29). Die ART-Kohorte wies ein günstiges kardiometabolisches Risikoprofil auf, das sich durch dünnere Hautfaltenmessungen, eine geringere Körperfettmasse und niedrigere Blutdruckwerte im Vergleich zu den spontan gezeugten Kindern auszeichnete (29). Zur Untersuchung langfristiger kardiovaskulärer Folgen analysierten Halliday et al. 193 ART- und 86 spontan gezeugte junge Erwachsene mit einem mittleren Alter von 27,0 und 26,9 Jahren (30). Die Auswertung des arteriellen Blutdrucks, der PWV und der cIMT ergab keine statistisch signifikanten Unterschiede zwischen ART- und spontan gezeugten Nachkommen, sodass die These eines ungünstigeren kardiovaskulären Risikoprofil der ART-Kohorte nicht unterstützt werden konnte (30). Eine große populationsbasierte Kohortenstudie in Norwegen, Schweden, Finnland und Dänemark verglich das Risiko, an kardiovaskulären Erkrankungen (CVD) (z.B koronarer Herzkrankheiten, Kardiomyopathie oder Herzinsuffizienz), Übergewicht und Typ-2-Diabetes zu erkranken, in einer Kohorte von 122.429 ART-Kindern und 7.574.685 Kontrollen (31). Die Ergebnisse legen nahe, dass ART-Kinder nicht statistisch signifikant häufiger an CVD oder Typ-2-Diabetes erkranken (31). Allerdings trat der kardiovaskuläre Risikofaktor Übergewicht bei ART-Kindern statistisch signifikant häufiger auf als bei spontan gezeugten Kindern (31). Eine australische Studie analysierte detailliert kardiometabolische Parameter, darunter Blutdruck, arterielle Gefäßsteifigkeit, anthropometrische Messungen sowie Lifestyle-Faktoren bei 163 ART-Jugendlichen und jungen Erwachsenen und 1.457 Kontrollen (32). Die Ergebnisse dieser Studie deuten auf ein ähnliches bzw. günstigeres kardiometabolisches Risiko in ART-Nachkommen im Vergleich zu den Kontrollen hin (32). ART-Jugendliche wiesen einen geringeren Body-Mass-Index, eine geringere arterielle Gefäßsteifigkeit und günstigere Blutfettwerte auf (32). Auch Shiloh et al. konnten keine statistisch signifikanten Unterschiede in der Häufigkeit von Hospitalisierungen aufgrund CVD in ART-Nachkommen im Vergleich zu spontan gezeugten Kontrollen feststellen (33).

2.4 Übergeordnete Fragestellung

CVD gehören zu den häufigsten Todesursachen weltweit (34). In der Literatur besteht eine uneinheitliche Datenlage zur kardiovaskulären Gesundheit von Kindern und Jugendlichen, die durch ART gezeugt worden sind. Dies unterstreicht die Notwendigkeit, diese Forschungslücke zu schließen und Individuen mit potenziell besonders hohem kardiovaskulärem Risiko zu identifizieren. Ziel der vorliegenden Arbeit ist eine umfassende prospektive Evaluation der vaskulären Morbidität von Kindern, Jugendlichen sowie jungen Erwachsenen, die durch ART gezeugt wurden. Der Fokus liegt auf dem Vergleich der vaskulären Gesundheit von ART- und spontan gezeugten Nachkommen sowie auf der Identifikation möglicher langfristiger kardiovaskulärer Risiken, einschließlich verfrühter vaskulärer Alterungsprozesse. Es wird zudem die Eignung spezifischer diagnostischer Methoden, wie der PWV und zweidimensionalen Speckle Tracking, zur Früherkennung vaskulärer Veränderungen bei ART-Nachkommen evaluiert.

3. Zusammenfassung

Mit der jährlich steigenden Anzahl von Kindern, die durch ART gezeugt wurden, rückt die langfristige und kurzfristige Gesundheit dieser Personen zunehmend in den Fokus. Aktuelle Studien äußern Bedenken hinsichtlich einer beeinträchtigten vaskulären Gesundheit bei ART-Kindern. Diese beinhalten eine generalisierte endotheliale Dysfunktion, eine erhöhte arterielle Steifigkeit und einen erhöhten Blutdruck. Im Gegensatz dazu konnten mehrere Studien diese Befunde nicht bestätigen und keine vaskulären Veränderungen bei ART-Kindern im Vergleich zu spontan konzipierten Kontrollen nachweisen. Eine verminderte vaskuläre Gesundheit trägt wesentlich zur Entwicklung von CVD bei, die eine der führenden Todesursachen unter den nicht übertragbaren Krankheiten darstellen. Eine frühzeitige und präzise Risikostratifizierung von Individuen mit potenziell erhöhtem kardiovaskulären Risiko ist daher von großer Bedeutung. Das Ziel der Forschung in den Artikeln „Vascular Health in Adults Born After Using Assisted Reproductive Technologies" und „Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness" war eine umfassende Untersuchung der vaskulären Gesundheit von ART-Nachkommen im Vergleich zu spontan konzipierten Altersgenossen. Zusätzlich war die Bewertung der PWV als Maß für die globale arterielle Steifigkeit sowie des zweidimensionalen Speckle Trackings der Aorta abdominalis und der Karotiden – eine neuartige Methode zur Bewertung der regionalen arteriellen Steifigkeit – von Interesse.

Beide Single-Center-Studien, deren Probanden vor allem aus der Metropolregion München stammten, hatten das Ziel einer präzisen und umfassenden Bewertung des Gefäßsystems. Dies umfasste die Erhebung anthropometrischer Variablen, der Vorerkrankungen, des Schwangerschaftsverlaufs und der Geburt, des mütterlichen Bildungsniveaus, der körperlichen Untersuchung sowie der Ernährungsqualität. Die Endothelfunktion wurde mithilfe des EndoPAT™ 2000-Geräts bewertet. Der brachiale Blutdruck, der zentrale Blutdruck und die PWV wurden mit einem oszillometrischen Blutdruckmessgerät aufgezeichnet. Die cIMT beider Arteriae carotis communis wurde sonografisch bestimmt. Darüber hinaus wurde nach einer Fastenperiode von ≥4 h ein laborchemisches, kardiometabolisches Risikoprofil erstellt. Das zweidimensionale Speckle Tracking der Aorta abdominalis und der Karotiden erfasste die regionale arterielle Steifigkeit von ART-Teilnehmern und spontan konzipierten Altersgenossen. Die globale arterielle Steifigkeit wurde mittels PWV gemessen.

Die Ergebnisse der Studie „Vascular Health in Adults Born After Using Assisted Reproductive Technologies“ zeigten keine statistisch signifikanten Unterschiede in der endothelialen Funktion, dem brachialen Blutdruck, dem zentralen Blutdruck, der PWV, der cIMT und dem Lipidprofil zwischen jungen Erwachsenen, die nach ART und solchen, die spontan gezeugt wurden. Die weitergehende Unterteilung in die Untergruppen der ART-Behandlungen zeigte ebenfalls keine statistisch signifikanten Unterschiede in den untersuchten Gefäßparametern zwischen den Kohorten der IVF-, ICSI- und spontan gezeugten Gruppen.

In der Studie „Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness" zeigte sich, dass die regionale und globale arterielle Steifigkeit bei den ART-Teilnehmern und ihren spontan konzipierten Altersgenossen statistisch nicht signifikant unterschiedlich war. Eine Subanalyse von Personen ≥10 Jahren, einschließlich einer Korrelationsanalyse, wurde durchgeführt, um den Einfluss des Alters auf die untersuchten Parameter zu evaluieren. Auch hierbei konnten keine statistisch signifikanten Unterschiede in der regionalen und globalen arteriellen Steifigkeit zwischen beiden Gruppen festgestellt. Interessanterweise war der brachiale systolische Blutdruck bei den ART-Teilnehmern tendenziell höher war als bei den Kontrollen. In den Korrelationen zwischen den beiden Gruppen zeigten sich keine statistisch signifikanten Unterschiede.

Insgesamt konnten beide Studien keine Beeinträchtigung der Gefäßfunktion bei ART-Nachkommen nachweisen. Es fanden sich keine Anzeichen für ein erhöhtes Risiko arterieller Steifigkeit im zunehmenden Alter bei ART-Nachkommen, da in den gemessenen Parametern keine statistisch signifikanten Unterschiede zu spontan konzipierten Kontrollen festgestellt wurden. Zukünftige Studien mit multizentrischem Design und größeren Stichprobengrößen sind erforderlich, um eine präzise kardiovaskuläre Risikostratifizierung der erwachsenen ART-Bevölkerung zu ermöglichen. Dies schließt auch eine Evaluation einer möglicherweise erhöhten kardiovaskulären Morbidität aufgrund verfrühter Gefäßalterung im Lebensverlauf ein.

4. Abstract

With a yearly increasing number of children born after using ART, the long- and short-term health of these individuals has become a subject of great interest. Recent studies have raised concerns about impaired vascular health in ART children, including generalized endothelial dysfunction, increased arterial stiffness, and elevated blood pressure. In contrast, several studies have failed to validate these findings and could not detect vascular modifications in ART children compared to spontaneously conceived controls. Decreased vascular health contributes significantly to the development of CVD, one of the leading causes of death among non-communicable diseases. Therefore, early and precise risk stratification of individuals with potentially increased morbidity seems beneficial. The objective of research in the articles "Vascular Health in Adults Born After Using Assisted Reproductive Technologies" and "Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness" was to conduct an extensive investigation into the vascular health of ART offspring compared to spontaneously conceived peers. Additionally, the evaluation of PWV as a measure for global arterial stiffness as well as two-dimensional speckle tracking of the abdominal aorta and both common carotid arteries, a novel method to assess regional arterial stiffness, was of particular interest.

Both single-center studies, whose participants primarily came from the greater Munich area, aimed for a precise and comprehensive evaluation of the vascular system. This included the assessment of anthropometric variables, prior medical history, course of pregnancy and birth, maternal educational level, physical examination, and diet quality. Endothelial function was assessed using the EndoPAT™ 2000 device. Brachial blood pressure, central blood pressure and PWV were recorded via an oscillometric blood pressure device. The cIMT of both common carotid arteries was determined sonographically. In addition, a cardiometabolic risk profile after a fasting period of ≥4 h was executed. Two-dimensional speckle tracking of the abdominal aorta and both common carotid arteries assessed regional arterial stiffness in ART subjects and spontaneously conceived peers. Global arterial stiffness was measured via PWV.

The study "Vascular Health in Adults Born After Using Assisted Reproductive Technologies" showed no statistically significant differences in endothelial function, brachial blood pressure, PWV, cIMT, or blood lipid levels between ART and spontaneously conceived young adults. Furthermore, no statistically significant differences in vascular function were found among the IVF, ICSI, and spontaneously conceived subgroups.

The results of the study “Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness” suggest no statistically significant difference in regional and global arterial stiffness between the ART subjects and their spontaneously conceived peers. A sub-analysis of subjects aged ≥10 years, including a correlation analysis, was performed to assess the influence of age on the studied parameters. No statistically significant differences in regional and global arterial stiffness were found between the two groups. Interestingly, brachial systolic blood pressure tended to be higher in ART subjects compared to controls. No statistically significant differences were observed in the correlations between the two groups.

In conclusion, both studies indicate that there is no impairment in vascular function in ART offspring. There is no evidence suggesting an increased risk of arterial stiffness with advancing age, as no statistically significant differences in parameters of arterial stiffness between ART subjects and spontaneously conceived peers were observed. Future studies with a multicenter design and greater sample sizes are required for a precise cardiovascular risk stratification of the adult ART population. This should also include an evaluation of potential increased cardiovascular morbidity due to premature vascular aging over the life course.

5. Originalarbeit I

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ORIGINAL ARTICLE

Vascular Health in Adults Born After Using Assisted Reproductive Technologies

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Abstract
An increasing number of children are conceived by assisted reproductive technologies (ART). Several studies indicated vascular alterations in ART children. However, limited data is available within the adult ART population. Therefore, this study investigated the overall vascular health of young ART adults in comparison to spontaneously conceived peers. In total, 16 ART subjects and 22 spontaneously conceived peers (22.06 ± 2.21 years vs. 22.00 ± 2.14 years, $p = 0.194$) were enrolled for the assessment of endothelial function, brachial blood pressure, central blood pressure, pulse wave velocity, carotid intima-media thickness, and blood lipids. No significant differences in vascular function were detected between the in vitro fertilization subgroup ($n = 9$), the intracytoplasmic sperm injection subgroup ($n = 7$) and spontaneously conceived peers. This pilot study suggests an unimpaired vascular function in young ART adults. In the future, multi-centric studies with a greater sample size are required to confirm the results of the current study and enable precise cardiovascular risk stratification of the adult ART population.

Keywords Vascular health · Endothelial function · Blood pressure · Arterial stiffness · Assisted reproductive technologies

Introduction

More than 8 million children have been born with the help of assisted reproductive technologies (ART) worldwide [1]. ART includes in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI), with or without cryopreservation of fertilized embryos.

Several studies have raised critical concerns about short- and long-term health consequences of children born via ART [2, 3]. Higher obstetric and perinatal risks like preterm birth, low birth weight, stillbirth, and perinatal mortality were described in children conceived by ART [1, 4–6]. Moreover, an increased risk for birth defects such as congenital heart defects or other major structural malformations was suggested among this cohort [4, 5, 7]. The long-term outcome of subjects conceived by ART has not been addressed yet but might include abnormalities in neurodevelopmental deficits, glucose metabolism, early development of metabolic syndrome and particularly alterations in the cardiovascular system [1, 5, 8].

According to Barker's 1990 hypothesis of "fetal programming of cardiovascular disease", adverse health events early in life might be linked to a higher cardiovascular risk at increased age [9]. In addition, environmental exposures in early life might have a long-lasting impact on the later health [1, 6].

Multiple studies were able to demonstrate that children and adolescents conceived by ART show structural and functional alterations of the vascular system [2, 3, 6, 10]. The generalized endothelial dysfunction and increased arterial stiffness shown in pediatric ART cohorts might induce prematurely elevated blood pressure [2, 3, 10]. Early vascular aging in ART conceived subjects could potentially lead to increased cardiovascular morbidity and mortality in adult life.

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In contrast, multiple pediatric studies could not demonstrate vascular modifications in ART children compared to spontaneously conceived controls [11, 12]. Moreover, a recent study conducted by Halliday et al. did not detect a significantly increased vascular or cardiometabolic risk in ART adults [13].

Limited data is available on the vascular function of adults who were conceived by ART [13]. Hence, this study aimed to investigate the overall vascular health of young ART adults in comparison to spontaneously conceived peers.

Materials and Methods

Ethical Statement

The study was approved on the 27th of December 2020 by the Ethics Committee of the Medical Faculty of the Ludwig Maximilians University Munich (Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilians-Universität München, Pettenkoferstraße 8a, 80336 Munich, Germany; approval number 20-0844) and was performed in accordance with the ethical standards of the Declaration of Helsinki. All participants gave their written informed consent to participate in the present study.

Study Design and Study Population

The recruitment of ART subjects was conducted in cooperation with the Division of Gynecological Endocrinology and Reproductive Medicine, Department of Obstetrics and Gynecology, University Hospital, LMU Munich (Munich, Germany). One hundred twenty-one couples whose children had been conceived by ART were informed in writing about the ongoing study. Only subjects conceived by IVF or ICSI were included in the present study. Healthy, spontaneously conceived peers were recruited via public calls within the greater Munich area. Study participants were enrolled between May 2021 and March 2022. For the present study, a minimum age of ≥ 18 years was required for participation. Both groups were matched by age and gender. Subjects with medical conditions that could potentially alter the vascular function were excluded from final analysis.

Medical History, Course of Pregnancy and Birth, Clinical Examination

Study participants were asked about pre-existing health conditions with a strong emphasis on cardiovascular morbidity (e.g., congenital heart disease, arterial hypertension, glucose metabolism disorders, lipid metabolism disorders). Smoking status and medications were recorded. The following information on the course of pregnancy and birth was retrospectively evaluated by screening clinical records and by questioning both parents: birth weight (g), birth height (cm), week of gestation (week), case of multiple pregnancy, maternal age at birth (years), maternal body mass index (BMI, kg/m^2) at conception, presence of gestational diabetes, maternal blood pressure during pregnancy ≥ 140/90 mmHg, and maternal smoking status during pregnancy. All study participants underwent a complete physical examination.

Diet Quality

High adherence to the Mediterranean diet was shown to be associated with reduced cardiovascular risk [14–16]. For the assessment of diet quality, the validated 14-Item Mediterranean Diet Assessment Tool established by Martínez-González et al. [14] was translated into German and provided to subjects. According to literature, low adherence to the Mediterranean diet was defined as a score ≤ 7 points and high adherence to the Mediterranean diet if a score ≥ 8 was present [14].

Physical Activity and Sedentary Behavior

The German version of the Global Physical Activity Questionnaire (GPAQ) developed by the World Health Organization (WHO) was applied to determine the level of physical activity in study participants [17]. Following the recommendations of the WHO, picture cards were presented for each activity domain [17]. Data cleaning was carried out in accordance with GPAQ recommendations [17]. For better comparability of physical activity level, total and recreational Metabolic-Equivalent-(MET)-min were calculated for each study participant [17]. WHO recommendations on physical activity were met if ≥ 600 total MET-min per week were achieved [17]. In addition, the amount of muscle strengthening activities per week as well as the time spent with sedentary activities per day were evaluated.

Anthropometric Variables

Body height and body weight of each subject was recorded in centimeters and kilograms, respectively. BMI was determined and weight classifications were defined as follows: underweight if BMI < 18.5 kg/m^2, normal weight if BMI ≥ 18.5 kg/m^2 but < 25 kg/m^2, overweight if BMI ≥ 25 kg/m^2 but < 30 kg/m^2, obese if BMI ≥ 30 kg/m^2. The gender-dependent, three-site skinfold protocol of Jackson-Pollock was applied using a skinfold caliper (Harpenden Skinfold Caliper, Baty International, UK) [18, 19]. Body fat percentage (BFP, %) was calculated using the corresponding software (Harpenden Caliper Body Assessment Software, version 1.0.0.17, Baty International, UK).

Endothelial Function

To assess endothelial function, the EndoPAT^{TM}2000 device (Itamar Medical, Israel) was utilized. Study participants were asked to fast ≥ 4 h and abstain from alcohol ≥ 24 h prior to the examination. Special care was taken that the room was quiet and temperature controlled. Before measurement, study participants had to remain in a supine and calm position for at least 15 min. To reduce measurement errors, study participants were asked to keep their fingers still during the entire examination period. The measurement was divided into a 5-min baseline recording period, a 5-min occlusion period and a 5-min post-occlusion period. For occlusion, a cuff was placed on the right upper arm and was inflated between 200 and 300 mmHg to guarantee a complete cessation of the blood flow. After successful examination, the software [version 3.7.2.(2.0)] automatically calculated the reactive hyperemia index (RHI) using the pre- and post-occlusion values.

Ambulatory Pulse Wave Analysis

Brachial systolic blood pressure (SBP, mmHg), brachial diastolic blood pressure (DBP, mmHg), mean arterial pressure (MAP, mmHg), heart rate (HR, bpm), central SBP (cSBP, mmHg), central DBP (cDBP, mmHg), augmentation index averaged to a heart rate of 75 bpm (AIx@75, %), and pulse wave velocity (PWV, m/s) were assessed using an oscillometric blood pressure device (Mobil-O-Graph®, IEM GmbH, Germany). In adult patients, central blood pressure and PWV assessed by the Mobil-O-Graph® were shown to be accurate and acceptable compared to intra-aortic measurements [20, 21]. Cuff sizes were selected according to right upper arm circumference. Before measurement, study participants had to remain in a supine and calm position for at least 5 min. In accordance with the recommendations of the European Society of Cardiology/European Society of Hypertension, three consecutive ambulatory measurements were performed and averaged to enhance data validity [22]. Elevated blood pressure was present if SBP was ≥ 130 mmHg and/or DBP was ≥ 85 mmHg [22].

Intima-Media Thickness of the Common Carotid Artery

Both common carotid arteries (CCA) were evaluated by one investigator for all study participants using a Philips iE33 xMatrix or a Philips Epiq 7G ultrasound device (Philips Healthcare, The Netherlands). Following the protocol of Dalla-Pozza et al. [23], both CCA were recorded in a supine position, the neck was extended up to a 45° angle and turned to the opposite side of examination. Using a 3–12 MHz linear array transducer, both CCA were evaluated in long axis view at level of carotid bifurcation. Three consecutive loops were acquired under three-lead ECG tracking. Recorded clips were transferred to a separate workstation (QLAB cardiovascular ultrasound quantification software, version 11.1, Philips Healthcare, The Netherlands) and analyzed by one investigator for all study participants. The carotid intima-media thickness (cIMT, mm) was measured semiautomatically at end-diastole (R wave in ECG) for the right and left side individually. The region of interest was set proximal of the carotid bifurcation and adjusted to 10 mm in length. Three measurements were performed, and an average was calculated for right and left cIMT individually. In addition, the left and right cIMT were averaged.

Cardiometabolic Risk Profile

Total cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), high density lipoprotein (HDL) cholesterol (mg/dL) and lipoprotein(a) [Lp(a), mg/dL] were assessed after a fasting period of ≥ 4 h. The following cut-off values were applied: total cholesterol ≥ 200 mg/dL, LDL cholesterol ≥ 116 mg/dL, HDL cholesterol for females ≤ 48 mg/dL and males ≤ 40 mg/dL, Lp(a) > 30 mg/dL. [24–26]

Statistical Analysis

Statistical analyses were performed using SPSS 27 (Release Date 2020, IBM SPSS Statistics for Windows, version 27.0.1.0, IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test, histograms and QQ-plots were used to test normality of continuous parameters. Nominal data was compared using the Pearson's Chi-squared test and Fisher's exact test. For continuous and normally distributed variables, the analysis of variance (ANOVA) was utilized. Non-normally distributed continuous variables were compared with the Kruskal–Wallis test. Data is given as mean ± SD for normally distributed parameters and as median (minimum/maximum) if non-normally distributed. A p-value < 0.05 was considered as statistically significant.

Results

Patients' Characteristics

For the present study, 17 ART subjects and 22 healthy controls were recruited. Within the ART cohort, one subject was excluded from final analysis due to history of T-cell lymphoma. In total, 16 ART subjects (IVF, $n = 9$; ICSI, $n = 7$) and 22 healthy controls were included for final analysis. The groups did not differ significantly in age and gender. Within the IVF group, one subject presented with bicuspid aortic valve, one with questionable history of myocarditis and one with Long QT syndrome. Two subjects took oral contraceptives. Within the ICSI group, one subject suffered from hypothyroidism. One subject was taking oral contraceptives, one thyroid medication and one methylphenidate. Among the control group, six subjects were taking oral contraceptives and one took bisoprolol due to recurrent migraine episodes.

A significant difference in weight classification was shown between all groups. However, after applying a pairwise post hoc test, no significant difference in weight classification was displayed between IVF subjects and controls as well as ICSI subjects and controls. IVF and ICSI subjects demonstrated a significantly higher BFP compared to controls (IVF $p = 0.047$; ICSI $p = 0.029$).

Compared to spontaneously conceived peers, birth weight ($p = 0.009$) and gestational age ($p = 0.029$) were significantly lower in IVF subjects. The number of multiple pregnancies differed significantly between all groups. By applying a pairwise post hoc test, a significantly higher number of multiple pregnancies was revealed in IVF subjects compared to spontaneously conceived peers ($p < 0.001$). In addition, ICSI subjects tended to have a higher number of multiple pregnancies compared to controls ($p = 0.051$). No significant differences in maternal age at birth and maternal BMI at conception were detected between all groups. None of the mothers had gestational diabetes, a blood pressure of ≥ 140/90 mmHg nor smoked during pregnancy.

The Fisher's exact test showed a significant difference in smoking status among the three groups ($p = 0.037$). However, after applying a pairwise post hoc test, smoking status did not differ between IVF subjects and controls as well as ICSI subjects and controls. There was no significant difference in dietary habits and physical activity level between all three groups.

Absolute values of blood lipids were not significantly different between all groups. A total cholesterol ≥ 200 mg/dL was present in one IVF subject, one ICSI subject and in five controls ($p = 0.854$). A LDL cholesterol ≥ 116 mg/dL was detected in two IVF subjects, two ICSI subjects and six controls ($p = 1$). There were 3 IVF subjects and 3 controls with a decreased HDL cholesterol ($p = 0.171$). A Lp(a) > 30 mg/dL was present in three IVF subjects, one ICSI subject and two controls ($p = 0.22$).

Detailed information on patients' characteristics is summarized in Table 1.

Endothelial Function

No significant difference in endothelial function was demonstrated between all groups (Table 2).

Ambulatory Pulse Wave Analysis

Ambulatory blood pressure and pulse wave analysis parameters did not show significant differences between groups. Detailed information on ambulatory blood pressure and pulse wave analysis parameters are demonstrated for the IVF, ICSI, and control group in Table 2.

Intima-Media Thickness of the Common Carotid Artery

Left, right, and averaged cIMT did not display significant differences between IVF, ICSI, and control subjects (Table 2).

Discussion

To the extent of our knowledge, this is one of the first studies aiming to investigate the overall vascular health of young adults conceived with the help of ART compared to spontaneously conceived peers. In total, 16 ART subjects (IVF, $n = 9$; ICSI, $n = 7$) and 22 age and gender matched controls were included in the present study.

Vascular Dysfunction and ART: Pathophysiological Considerations

In previous studies, children and adolescents conceived by ART displayed premature vascular aging [2, 3, 10]. This was visualized by a significantly increased PWV and cIMT as well as a significantly reduced flow mediated dilation [2, 3, 10]. As data of Scherrer et al. suggest, arterial hypertension could count as one of the first ART-related signs of vascular dysfunction [10]. In addition, it is thought that the endothelial dysfunction in ART children is not only limited to the systemic circulation but also takes place in pulmonary vessels [2]. The present study was not able to prove the above-mentioned findings in adult ART subjects: All vascular parameters including endothelial function, brachial blood pressure, central blood pressure, PWV, and cIMT did not show significant differences between IVF subjects, ICSI subjects and controls. These results are consistent with previous findings of Halliday et al. [13]. The authors conducted a large cohort study, in which 193 ART subjects and 86 spontaneously conceived peers (mean age: 27.5 ± 2.8 years vs. 27.6 ± 2.6 years, $p = 0.76$) were enrolled [13]. Subjects underwent a detailed cardiovascular evaluation, including the assessment of anthropometric measures, blood pressure, PWV, cIMT, and various metabolic markers [13]. Similarly, to the present study, Halliday et al. demonstrated no evidence of impaired cardiovascular function in the adult ART cohort [13]. Likewise, pediatric studies suggest that children

Table 1 Patients' characteristics in the IVF, ICSI, and control group

Variable	IVF ($n=9$)	ICSI ($n=7$)	Control ($n=22$)	p-value
Age (years)	20.97 ± 2.56	21.17 ± 1.86	22.00 ± 2.14	0.427
Female (*n* (%))	7 (77.8)	5 (71.4)	14 (63.6)	0.89
Bodyweight (kg)	67.63 ± 12.21	67.41 ± 10.15	67.61 ± 8.84	1.00
Height (cm)	172.50 ± 8.21	168.37 ± 7.98	175.81 ± 7.83	0.10
BMI (kg/m^2)	22.16 (16.79/26.32)	23.78 (20.83/27.44)	21.59 (18.93/28.50)	0.17
Weight classification				
Underweight (*n* (%))	1 (11.1)	0 (0)	0 (0)	0.027*
Normal weight (*n* (%))	5 (55.6)	5 (71.4)	21 (95.5)	
Overweight (*n* (%))	3 (33.3)	2 (28.6)	1 (4.5)	
Body fat percentage (%)	29.39 ± 8.12[a]	30.82 ± 5.46[a]	21.57 ± 8.19	0.008**
Course of pregnancy and birth				
Birth weight (g)[1]	2995 (610/3240)[b]	3020(1940/3400)	3420 (1810/4420)	0.007**
Birth height (cm)[2]	51.0 (48.0/54.0)	50.5 (44.0/52.0)	51.00 (43.0/56.0)	0.679
Gestational age (weeks)[1]	37.0 (27.0/39.0)[c]	39.0 (33.0/41.0)	39.0 (33.0/41.0)	0.031*
Maternal age at birth (years)[3]	34.93 ± 2.82	33.53 ± 5.08	32.09 ± 3.34	0.135
Maternal BMI at conception (kg/m^2)	22.66 ± 2.95	23.69 ± 2.44	21.84 ± 2.18	0.209
Multiple pregnancy (*n* (%))	5 (55.6)[d]	0 (0)	0 (0)	< 0.01**
Smoking, diet quality, and physical activity				
Smoking (*n* (%))	1 (11.1)	2 (28.6)	0 (0)	0.037*
MEDAS	6.56 ± 2.30	5.29 ± 2.93	7.27 ± 1.67	0.10
≥ 600 total MET-min per week (*n* (%))[4]	8 (100)	7 (100)	21 (95.5)	1
≥ 600 recreational MET-min per week (*n* (%))[5]	7 (87.5)	4 (66.7)	18 (81.0)	0.701
Muscle strengthening activities (times/week)[4]	2.0 (0.0/5.5)	1.0 (0.0/ 2.0)	2.0 (0.0/4.0)	0.301
Sedentary behavior (min/day)	383.33 ± 125.30	514.29 ± 176.15	409.09 ± 139.35	0.170
Cardiometabolic risk profile				
Total cholesterol (mg/dL)	171.0 (136/282)	177.0 (143/207)	172.0 (131/243)	0.723
Increased total cholesterol (*n* (%))	1 (11.1)	1 (14.3)	5 (22.7)	0.854
LDL (mg/dL)	94.33 ± 27.17	98.29 ± 15.16	102.27 ± 23.44	0.680
Increased LDL (*n* (%))	2 (22.2)	2 (28.6)	6 (27.3)	1
HDL (mg/dL)	57.0 (35/148)	65.0 (49/107)	61.5 (37/95)	0.773
Decreased HDL (*n* (%))	3 (33.3)	0 (0)	3 (13.6)	0.171
Lp(a) (mg/dL)	5.0 (5/84)	5.0 (5/64)	6.0 (5/98)	0.568
Increased Lp(a) (*n* (%))	3 (33.3)	1 (14.3)	2 (9.1)	0.22

IVF In vitro fertilization; *ICSI* Intracytoplasmic sperm injection; *BMI* Body mass index; *MEDAS* Mediterranean diet adherence score; *MET* Metabolic-equivalent; *LDL* Low-density lipoprotein; *HDL* High-density lipoprotein; *Lp(a)* Lipoprotein(a). [1]18 controls, 8 IVF subjects, and 6 ICSI subjects were included in the analysis. [2]18 controls, 6 IVF subjects, and 6 ICSI subjects were included in the analysis. [3]6 ICSI subjects were included in the analysis.[4]8 IVF subjects were included in the analysis. [5]8 IVF subjects and 6 ICSI subjects were included in the analysis. [a]IVF differs significantly from control ($p=0.047$), ICSI differs significantly from control ($p=0.029$). [b]IVF differs significantly from control ($p=0.009$). [c]IVF differs significantly from control ($p=0.029$). [d]IVF differs significantly from control ($p<0.001$). Data is given as mean ± SD for normally distributed parameters and as median (minimum/maximum) if non-normally distributed. *$p<0.05$. **$p<0.01$

conceived by ART are not at increased cardiovascular risk [11, 12]. A population-based cohort study evaluated the risk of cardiovascular disease or type 2 diabetes in 122,429 ART children and 7,574,685 spontaneously conceived peers from Norway, Sweden, Finland, and Denmark [11]. Interestingly, the authors could not demonstrate a statistically significant difference in the incidence of cardiovascular disease or type 2 diabetes between ART children and spontaneously conceived peers [11]. However, ART children demonstrated a significantly higher risk for obesity [11]. A retrospective Israeli study evaluated hospitalizations due to cardiovascular disease of children born following fertility treatment up to 18 years of age [12]. 2603 IVF subjects, 1721 subjects born as a result of ovulation induction and 237,863 spontaneously conceived peers were included in this study [12]. In comparison to the spontaneously conceived group, no elevated risk of long-term pediatric cardiovascular disease was displayed in the fertility treatment group [12]. The studies of Halliday

Table 2 Vascular function in the IVF, ICSI, and control group

Variable	IVF ($n=9$)	ICSI ($n=7$)	Control ($n=22$)	*p*-value
Endothelial function				
RHI[1]	1.96 (1.39/2.89)	2.42 (1.49/3.34)	1.86 (1.37/5.09)	0.567
Ambulatory pulse wave analysis				
SBP (mmHg)	127.81 ± 10.26	120.24 ± 5.42	122.02 ± 7.01	0.104
Elevated SBP (*n* (%))	4 (44.4)	0 (0)	3 (13.6)	0.056
DPB (mmHg)	72.70 ± 7.76	74.14 ± 6.65	73.86 ± 7.89	0.913
Elevated DBP (*n* (%))	1 (11.1)	1 (14.3)	0 (0)	0.171
MAP (mmHg)	98.15 ± 7.84	95.24 ± 4.80	95.77 ± 6.77	0.617
cSBP (mmHg)	113.85 ± 9.17	110.79 ± 5.39	109.85 ± 7.04	0.396
cDBP (mmHg)	74.48 ± 7.98	76.50 ± 7.09	75.29 ± 7.94	0.877
Heart rate (bpm)	65.00 ± 12.83	80.38 ± 16.39	67.48 ± 13.56	0.073
AIx@75 (%)	10.74 ± 10.32	17.29 ± 14.17	11.85 ± 10.72	0.470
PWV (m/s)	5.16 ± 0.40	5.05 ± 0.28	5.13 ± 0.32	0.813
Intima-media thickness of the common carotid artery				
Left cIMT	0.46 (0.40/0.53)	0.43 (0.40/0.48)	0.44 (0.40/0.56)	0.367
Right cIMT[2]	0.44 (0.40/0.49)	0.41 (0.40/0.59)	0.46 (0.40/0.57)	0.264
Averaged cIMT[2]	0.45 (0.40/0.51)	0.44 (0.41/0.50)	0.45 (0.41/0.55)	0.624

IVF In vitro fertilization; *ICSI* Intracytoplasmic sperm injection; *RHI* Reactive hyperemia index; *SBP* Systolic blood pressure; *DBP* Diastolic blood pressure; *MAP* Mean arterial pressure; *cSBP* Central systolic blood pressure; *cDBP* Central diastolic blood pressure; *AIx@75* Augmentation index averaged to a heart rate of 75 bpm; *PWV* Pulse wave velocity; *cIMT* Carotid intima-media thickness. [1]8 IVF subjects were included in the analysis. [2]21 controls and 5 ICSI subjects were included in the analysis. Data is given as mean ± SD for normally distributed parameters and as median (minimum/maximum) if non-normally distributed

et al. [13] and Shiloh et al. [12] support the cardiovascular findings of the present study.

Within literature, the following pathophysiological considerations have been reported to impair the vascular health of ART offspring:

While age, gender, diet quality, physical activity level, and blood lipids did not differ significantly between the studied groups, it should be noted that the ART cohort displayed a higher prevalence of smokers and a significantly higher BFP. These cardiovascular risk factors could have potentially negatively influenced the vascular health of the studied ART cohort.

Both Barker's hypothesis of "fetal programming of cardiovascular disease" and the "developmental origins of adult disease" hypothesis link adverse environmental influences during early human development to an increased risk of non-communicable diseases, such as cardiovascular disease, later in life [9, 27]. "At-risk" pregnancies caused by maternal obesity, maternal overnutrition, gestational weight gain, maternal cardiovascular disease or advanced maternal age might represent such environmental influences [27]. As advanced age and pre-existing cardiovascular diseases negatively affect fertility, individuals with such risk factors might require ART more often. The literature suggests that the prevalence of parental cardiovascular diseases and risk factors, such as hypertension, hyperlipidemia, or diabetes, negatively impact the offspring's cardiovascular morbidity [28]. Additionally, animal models revealed that advanced maternal age might lead to increased long-term cardiovascular health risks for the offspring [29]. Epidemiological and human studies support these findings [29]. In the present study, neither maternal age at birth, maternal BMI at conception, the prevalence of gestational diabetes nor hypertension during pregnancy differed significantly between the groups.

The ART procedure itself represents an extreme exposure to environmental stimuli for the gamete and embryo, which might result in epigenetic modifications of the DNA potentially causing long lasting alterations of the vascular structure and function [30]. Oxidative stress (OS) is considered to be one possible cause for these epigenetic changes [1]. During the ART procedure, an excess of OS might be present due to a lack of natural antioxidant systems and dysregulation of OS production. In the short-term, OS might cause epigenetic modifications in the DNA [1] and in long-term, studies on animal models propose endothelial dysfunction and hypertension as possible outcomes [1]. In the embryonic development, the cardiovascular system is one of the first to be matured and thus, is proposed to be severely damaged by OS [1]. Increased levels of OS are associated with ART and pregnancies "at risk" (e.g., women of advanced age, obese women, hypertensive disorders of pregnancy, gestational diabetes, and preterm birth) [1]. These risk factors might harm the offspring's cardiovascular function through increased OS levels [31, 32]. Compared to healthy peers, IVF subjects displayed a lower birthweight, a lower gestational age, and an increased number of multiple pregnancies. Hence, the ART cohort was potentially exposed to higher OS levels early in life.

This pilot study demonstrated that the overall vascular function in ART is not significantly altered in comparison to spontaneously conceived peers. In line with previous findings [13], this study suggests that adults conceived by ART are not necessarily at higher cardiovascular risk. Significant differences in some cardiovascular and perinatal risk factors which might lead to a decreased vascular function at advanced age were displayed. Hence, further studies with larger sample sizes are required to determine potential ART risk groups. An ART follow-up study might be beneficial to assess the extent of increased cardiovascular morbidity and to evaluate the potential process of vascular aging over the life span.

Limitations

The present study was designed as a single-center study. ART subjects were recruited from one fertility center within Germany. The sample size of the present study can be considered as rather small and heterogeneous. Hence, the assessment of specific cardiovascular risk groups within the ART cohort was not applicable.

Adverse perinatal conditions (e.g., premature birth, multiple pregnancies) were intentionally not defined as exclusion criteria in this study. Preliminary exclusion of such participants was thought to have a positive impact on the 'actual' cardiovascular risk profile of the studied ART population as well as substantially restrict the sample size of this single-center study. Hence, further multi-centric studies with a longitudinal study design and larger sample sizes are required for an extensive cardiovascular risk stratification of the adult ART population. Additionally, the ART group studied was at young adult age and vascular changes might only be assessed at a more advanced age.

The results of this study might be attributed to lifestyle habits, parent-related influence, the ART procedure itself or a combination of these factors. Diet quality and physical activity did not differ significantly between all three groups. Even though, no significant impairments of vascular function were detected between all groups, the significantly higher BFP and the higher amount of smokers might have had negative effects on the vascular health of the ART group.

Detailed exploration of maternal cardiovascular risk factors prior to pregnancy and determination of its influence on the offspring's vascular health seems beneficial. Data on pregnancy and birth was retrospectively evaluated by screening clinical records and by interviewing both parents. For some study participants this data was not complete as clinical records were missing or incompletely filled out by previous medical professionals.

Subjects were required to fast ≥ 4 h and not to drink alcohol ≥ 24 h before study participation. However, a stricter standardization of diet and physical activity of at least ≥ 12 h prior to the vascular measurements should be applied in future studies. In literature, a reduction in SBP and DBP after exercise is defined as post-exercise hypotension [33]. The duration of this phenomenon is described to last between 2 and 13 h post-exercise [33]. Therefore, future studies should consider this potential cofounder and adjust their study design accordingly.

As the investigators of the current study were not blinded, the results may have been influenced, in particular the evaluation of cIMT. In contrast, various vascular parameters (e.g., RHI, blood pressure) were assessed automatically by devices.

Conclusion

This pilot study investigated the vascular health of 16 young ART adults. In contrast to previous studies, the present study was not able to detect any significant differences in vascular function between ART subjects and spontaneously conceived peers. The results of this study might weaken previous ART health concerns which have been raised over the past years. In the future, multi-centric studies with a greater sample size are required to confirm the results of the current study and enable precise cardiovascular risk stratification of the adult ART population.

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Declarations

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6. Originalarbeit II

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Subjects Conceived through Assisted Reproductive Technologies Display Normal Arterial Stiffness

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Abstract: Multiple studies reported signs of vascular dysfunction in subjects conceived through assisted reproductive technologies (ART). The assessment of arterial stiffness in this cohort seems beneficial for risk stratification. Regional arterial stiffness of the abdominal aorta (AAO) and the common carotid arteries (CCA) was evaluated sonographically using two-dimensional speckle tracking in subjects conceived through ART and spontaneously conceived peers. Global arterial stiffness was assessed utilizing an oscillometric blood pressure device. The cohorts of 67 ART subjects and 86 spontaneously conceived peers (11.31 (8.10–18.20) years vs. 11.85 (8.72–18.27) years, $p = 0.43$) did not differ significantly in parameters of regional and global arterial stiffness. In the sub-analysis of study participants ≥10 years of age, markers of arterial stiffness did not display significant differences between both groups. However, a higher tendency of brachial systolic blood pressure was demonstrated in the ART cohort compared to the control group (120.18 ± 9.57 mmHg vs. 116.55 ± 8.05 mmHg, $p = 0.050$). The present study displayed no significant differences in arterial stiffness between ART subjects and spontaneously conceived peers. Moreover, this study suggests that arterial stiffness does not elevate more profoundly in ART subjects with increasing age. Further studies are required for a more detailed cardiovascular risk stratification of the ART cohort.

Keywords: assisted reproductive technologies; abdominal aorta; common carotid artery; two-dimensional speckle tracking; arterial stiffness; peak circumferential strain; pulse wave velocity

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1. Introduction

Arterial stiffness plays an important role in the pathophysiology of cardiovascular disease (CVD) and is involved in the onset of coronary heart disease, heart failure and stroke [1–5]. Increased arterial stiffness is considered to be an independent cardiovascular risk factor leading to elevated morbidity and mortality [5,6].

Arterial stiffening is characterized by increased functional rigidity and reduced elasticity of the vessel's walls [4]. This degenerative process can be induced by age or through atherosclerosis [4,7]. The stiffening of the arteries leads to an augmentation of blood pressure, left ventricular afterload and a decrease in coronary perfusion [2,8].

Assisted reproductive technologies (ART) are defined as fertility-related treatments in which eggs or embryos are handled [9]. ART encompasses procedures such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), or gamete intrafallopian transfer (GIFT) [9]. More than ten million children worldwide and about three percent of children in Germany have been conceived after using ART [10,11]. According to the "developmental origins of adult disease" hypothesis, the offspring is at higher risk to develop a non-communicable disease such as CVD after being exposed to adverse environmental influences (e.g., maternal obesity, advanced maternal age, gestational weight gain, pre-existing maternal CVD) [12]. During the pregnancy itself, an increased maternal CVD risk might be present if hypertensive disorders of pregnancy or gestational diabetes are present [13]. Therefore, cardiovascular risk factors of parents need to be considered, as they can negatively influence the future offspring's cardiovascular health [14].

There is contradictory evidence on cardiovascular health of ART subjects. Several studies consider early vascular alterations in subjects conceived after using ART, potentially leading to increased cardiovascular morbidity and mortality later in life, as possible long-term health consequences [15–17]. A meta-analysis conducted by Guo et al. revealed a significantly increased blood pressure, suboptimal cardiac diastolic function and elevated vessel thickness as a conspicuous cardiovascular risk profile of the ART offspring [18]. In contrast, Halliday et al. could not demonstrate an elevated cardiometabolic risk in a cohort of 193 ART adults aged 22 to 35 years [19]. Consequently, the cardiovascular morbidity of the ART offspring remains unclear and requires further research.

As CVD counts as one of the leading causes of death by non-communicable diseases worldwide [20], the early detection of subtle vascular alterations can be regarded as crucial to improve the overall patient outcome. In the past, multiple methodologies were introduced to assess arterial stiffness non-invasively [2]. Recently, two-dimensional speckle tracking (2DST) has been established as a novel method to evaluate regional arterial stiffness sonographically [21]. Interestingly, in subjects with and without hypertension, 2DST appeared to be superior to conventional measures and showed a better reproducibility [21,22].

To the best of our knowledge, 2DST has not been applied yet to assess arterial stiffness in ART offspring. Hence, this study aimed to investigate whether subtle changes in regional arterial stiffness can be visualized by 2DST of the abdominal aorta (AAO) and the common carotid arteries (CCA) in ART subjects compared to spontaneously conceived peers. Moreover, pulse wave velocity (PWV, m/s), a marker of global arterial stiffness, was assessed in all study participants via an oscillometric blood pressure device.

2. Materials and Methods

2.1. Ethical Statement

The study was performed in accordance with the ethical standards of the Declaration of Helsinki. The Ethics Committee of the Medical Faculty of the Ludwig Maximilians University Munich (Munich, Germany) approved this study (protocol code: 20-0844, date of approval: 27 December 2020). All participants gave their written informed consent to participate in the present study. For minor study participants, prior written informed consent was additionally given from parents or legal guardians.

2.2. Study Design and Study Population

A cohort of 156 study participants were recruited from the Munich heARTerY-study (Assisted Reproductive Technologies and their effect on heart and arterial function in Youth) between May 2021 and March 2022. The cohort consisted of 70 subjects who were conceived after using assisted reproductive technologies and 86 spontaneously conceived peers. To additionally assess the influence of age on the cardiovascular parameters studied, subjects of different ages (children, adolescents, young adults) were included. ART subjects were recruited in cooperation with the Division of Gynecological Endocrinology and Reproductive Medicine, Department of Obstetrics and Gynecology, University Hospital, LMU Munich. Healthy age- and gender-matched controls without known cardiovascular conditions, who were conceived spontaneously, were acquired through public calls within the greater Munich area.

2.3. Assessment of Anthropometric Variables

Bodyweight (kg), body height (cm) and body mass index (BMI, kg/m^2) were determined. Weight classifications were defined in minors as follows: underweight if <10 percentile (P.), normal weight if ≥10 P. but <90 P., overweight if ≥90 P., obese if ≥97 P. [23]. Weight classifications for participants ≥ 18 years of age were defined as: underweight if BMI < 18.5 kg/m^2, normal weight if BMI ≥ 18.5 kg/m^2 but < 25 kg/m^2, overweight if BMI ≥ 25 kg/m^2 but <30 kg/m^2, obese if BMI ≥ 30 kg/m^2.

2.4. Medical History, Course of Pregnancy and Birth, Maternal Educational Level, Physical Examination

Pre-existing health conditions, smoking status and the regular use of medication was evaluated. Data on pregnancy and birth was assessed retrospectively by screening clinical records and by questioning both parents. The following parameters were included in the final analysis: birth weight (g), birth height (cm), gestational age (week), case of multiple pregnancy, maternal age at birth (years), maternal BMI at conception (kg/m^2), presence of gestational diabetes and maternal blood pressure during pregnancy ≥ 140/90 mmHg. In addition, maternal educational level was assessed according to the German educational system: no school leaving qualification (0), lower secondary school leaving certificate (1), intermediate secondary school leaving certificate (2), general qualification for university entrance (3), completed apprenticeship (4), completed university degree (5). Further, a physical examination was executed in all study participants.

2.5. Assessment of Diet Quality

High adherence to the Mediterranean diet is associated with a positive effect on cardiovascular health [24,25]. In this study, the validated 14-item Mediterranean diet assessment tool by Martínez-González et al. was applied for adult participants [24]. For participants < 18 years, the KIDMED index by Serra-Majem et al. was used [26]. Both questionnaires were translated into German. A score ≥ 8, was considered as high adherence to the Mediterranean diet [24,26].

2.6. Vascular Assessment

2.6.1. Ambulatory Blood Pressure Measurement

Brachial systolic blood pressure (SBP, mmHg), brachial diastolic blood pressure (DBP, mmHg) and pulse wave velocity (PWV, m/s) were assessed using an oscillometric blood pressure device (Mobil-O-Graph®, IEM GmbH, Aachen, Germany). Oscillometric assessed PWV by the Mobil-O-Graph® displayed acceptable accuracy compared to intra-aortic readings in adult patients [27]. Moreover, pediatric reference values were established in the past [28]. Cuff sizes were selected in accordance with right upper arm circumference. Study participants had to remain in a supine and calm position for at least five minutes before measurement. In accordance with the recommendations of the American College of Cardiology and American Heart Association, three consecutive ambulatory measurement were performed and averaged to enhance data validity [29].

2.6.2. Peak Circumferential Strain, Peak Strain Rate and Arterial Distensibility of the Abdominal Aorta and the Common Carotid Arteries

Sonography of the abdominal aorta (AAO) and both common carotid arteries (CCA) was performed by one investigator for all study participants. A Philips iE33 xMatrix or a Philips Epiq 7G ultrasound device (Philips Healthcare, Amsterdam, The Netherlands) was used for sonographic examination. The AAO was evaluated using either a 3–8 MHz sector or a 1–5 MHz sector array transducer in short subxiphoid view at epigastric level. Both CCA were recorded in a supine position. The neck was extended up to a 45° angle and turned to the opposite side of examination. The area right below the carotid bifurcation was examined using a 3–8 MHz sector array transducer in short axis view. Three consecutive loops were recorded under three-lead ECG tracking and transferred to a separate workstation (QLAB cardiovascular ultrasound quantification software, version 11.1, Philips Healthcare, Amsterdam, The Netherlands).

Offline analysis was performed by one investigator for all study participants. The software's SAX-A function was used. The smallest region of interest (ROI) was set to precisely track the vessel's wall. Special care was taken to avoid tracking of the perivascular tissue. The software then tracked pixels of the ROI two-dimensionally over the cardiac cycle and quantified their deformation in percent (Figure 1) [22].

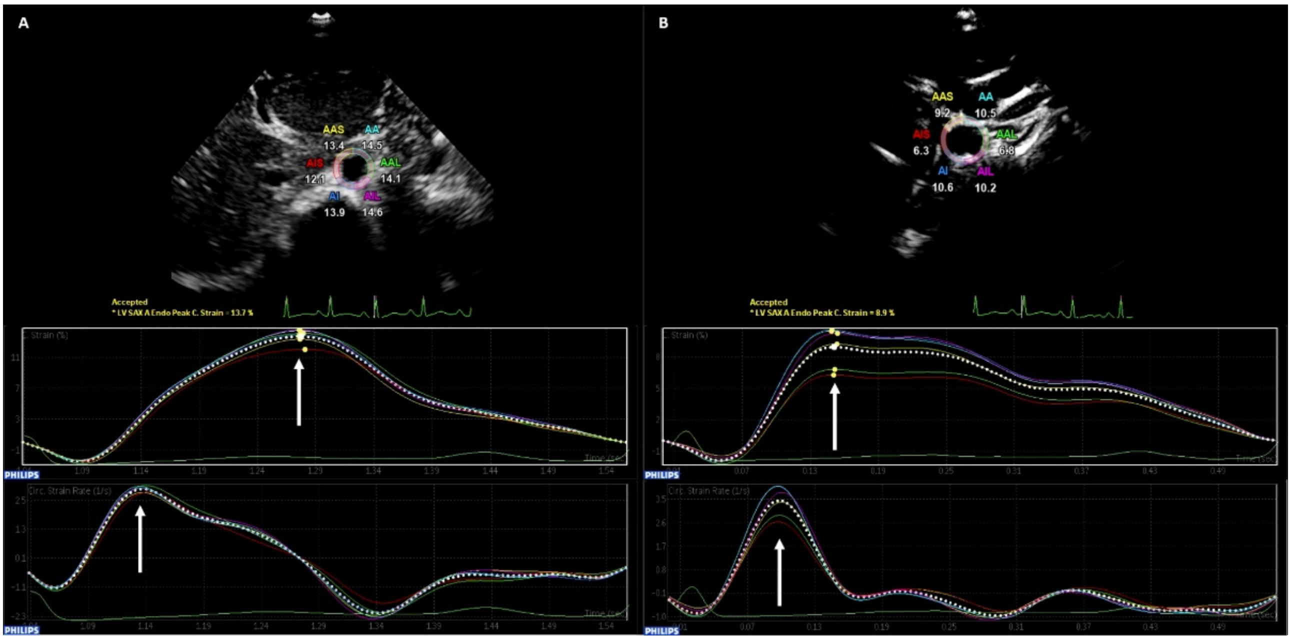

Figure 1. Two-Dimensional Speckle Tracking (2DST) of the Abdominal Aorta and the Common Carotid Arteries. 2DST tracks pixels of the region of interest (ROI) over the cardiac cycle and quantifies their deformation in percent. Special care was taken to set the ROI as small as possible to precisely track the vessel's wall. Peak circumferential strain (upper graph, marked with the arrow, %) and peak strain rate (lower graph, marked with the arrow, 1/s) were identified manually. (**A**) The abdominal aorta (AAO) was evaluated in short subxiphoid view at epigastric level under three-lead ECG tracking. (**B**) Both common carotid arteries (CCA) were recorded under three-lead ECG tracking in supine position. The neck extended up to a 45°angle and turned to the opposite side of examination.

The following parameters were identified manually for AAO and both CCA individually: peak circumferential strain (CS, %), peak strain rate (SR, 1/s) (Figure 1). An average of three measurements was calculated to enhance data validity.

Arterial distensibility (Dis, $\text{mmHg}^{-1} \times 10^{-3}$) was defined as follows [30]:

$$\text{Arterial Distensibility} = \frac{(2 \times \text{ CS})}{\text{SBP} - \text{DBP}}.$$

SBP and DBP assessed by the Mobil-O-Graph® were utilized for this calculation. Dis was calculated for the AAO and for both CCA individually.

2.6.3. Stiffness Index β

The abovementioned sonographic study protocol was applied. M-Mode of the AAO was performed in short axis view under three-lead ECG tracking using a 3–8 MHz sector or a 1–5 MHz sector array transducer. M-Mode of both CCA was carried out in long axis view under three-lead ECG tracking utilizing a 3–12 MHz linear array transducer.

For all study participants, the end-diastolic diameter (dD, mm) and the end-systolic diameter (sD, mm) of the AAO and both CCA were measured offline (IntelliSpace Cardiovascular Ultrasound Viewer, Philips Healthcare, Amsterdam, The Netherlands) by one investigator.

The stiffness index β (unitless) was calculated for the AAO in short axis and for both CCA in long axis as [7]:

$$\text{Stiffness Index } \beta = \frac{\ln\left(\frac{SBP}{DBP}\right)}{\Delta D/dD}.$$

ΔD (mm) was defined as the difference of sD and dD. SBP and DBP assessed by the Mobil-O-Graph® were utilized for this calculation.

2.7. Statistical Analysis

Statistical analysis was performed using SPSS 27 (Release Date 2020, IBM SPSS Statistics for Windows, version 27.0.1.0, IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test, the Kolmogorov–Smirnov test, histograms and QQ-plots were used to test normality of continuous parameters. For continuous and normally distributed variables the unpaired *t*-test was utilized. If continuous data was non-normally distributed the Mann–Whitney U test was applied. Data is given as mean ± SD for normally distributed parameters and as median (interquartile range, IQR) if non-normally distributed. Pearson correlations coefficient was used for normally distributed variables and Spearman correlations coefficient for non-normally distributed variables. For the statistical comparison of correlations, the free cocor software package (http://comparingcorrelations.org/ accessed on 17 October 2022) was used [31]. A p-value < 0.05 was considered as statistically significant.

3. Results

3.1. Patients' Characteristics

For this study 70 ART and 86 spontaneously conceived peers were recruited. Within the ART cohort, one patient was excluded from further analysis due to history of T-cell lymphoma and one due to history of heart surgery. In addition, one ART subject was excluded due to incomplete data assessment. In total, 67 ART subjects (50 ICSI, 16 IVF, 1 GIFT) and 86 spontaneously conceived peers were included in the final analysis.

Within the ART group, one subject displayed with long QT syndrome, one with a bicuspid aortic valve, one with questionable history of myocarditis, one with hypothyroidism and one with history of hypercholesterolemia. Four ART subjects used oral contraceptives, one was taking L-Thyroxine and one methylphenidate.

Within the control group, six subjects were taking oral contraceptives, one subject was taking bisoprolol due to recurrent migraine episodes and one was taking methylphenidate.

Both groups did not differ significantly in age, gender, bodyweight, body height, BMI and smoking status. Compared to the spontaneously conceived peers, birth weight, birth height and gestational age of ART subjects were significantly lower, whereas the number of multiple pregnancy and maternal age at birth were significantly higher in the ART group. Maternal BMI at conception, presence of gestational diabetes, maternal blood pressure during pregnancy $\geq$ 140/90 mmHg and maternal educational level did not differ significantly between both groups. No significant difference in adherence to the Mediterranean diet was demonstrated between ART subjects and spontaneously conceived peers. ART adults tended to have a lower adherence to the Mediterranean diet compared to controls. Detailed information on patients' characteristics is summarized in Table 1.

3.2. Vascular Function

When vascular function was analyzed, no significant differences were detected between both groups. Table 2 summarizes data on vascular function for the ART and control group.

3.3. Influence of Age on Vascular Function

To assess the influence of age on the cardiovascular parameters studied, a sub-analysis of subjects $\geq$ 10 years of age was conducted. Moreover, a correlation analysis was performed to assess the influence of age on the cardiovascular parameters studied.

Table 1. Patients' Characteristics in the ART and Control Group.

Variable	ART (n = 67)	Control (n = 86)	*p*-Value
Age (years)	11.31 (8.10–18.20)	11.85 (8.72–18.27)	0.43
Female (n (%))	39 (58.2)	44 (51.2)	0.39
Bodyweight (kg)	38.70 (23.40–58.80)	42.70 (29.05–59.25)	0.25
Body height (cm)	145.00 (125.00–167.00)	157.00 (133.38–170.25)	0.11
BMI (kg/m^2)	16.79 (15.09–20.83)	17.66 (15.43–21.05)	0.49
Weight classification			1
Underweight (n (%))	4 (6.0)	6 (7.0)	
Normal weight (n (%))	58 (86.6)	74 (86.0)	
Overweight (n (%))	5 (7.5)	6 (7)	
Smoking (n (%))	3 (4.5)	2 (2.3)	0.65
Course of Pregnancy and Birth, Maternal Educational Level			
Birth weight (g) [1]	2990 (2405–3243)	3440 (3210–3670)	<0.001 ***
Birth height (cm) [2]	50 (48–52)	52 (50–54)	<0.001 ***
Gestational age (weeks) [3]	38 (36–40)	39 (38–40)	<0.001 ***
Multiple pregnancy (n (%))	21 (31.3)	2 (2.3)	<0.001 ***
Maternal age at birth (years) [4]	35.37 ± 3.72	33.07 ± 4.10	<0.001 ***
Maternal BMI at conception (kg/m^2) [5]	22.49 (20.55–24.65)	21.38 (20.24–22.72)	0.09
Gestational diabetes (n (%)) [6]	3 (5.3)	3 (4.2)	1
Maternal blood pressure during pregnancy ≥ 140/90 mmHg (n (%)) [7]	0 (0)	3 (6.4)	0.29
Maternal educational level [8]	4 (3–5)	5 (4–5)	0.22
Diet Quality			
MEDAS [9]	5.94 ± 2.51	7.27 ± 1.67	0.05
KIDMED [10]	6.24 ± 2.33	6.92 ± 2.11	0.11

ART = assisted reproductive technologies; BMI = body mass index. [1] 65 ART subjects and 79 control subjects were included in the analysis. [2] 63 ART subjects and 79 control subjects were included in the analysis. [3] 62 ART subjects and 77 control subjects were included in the analysis. [4] 66 ART subjects were included in the analysis. [5] 47 ART subjects and 61 control subjects were included in the analysis. [6] 57 ART subjects and 71 control subjects were included in the analysis. [7] 28 ART subjects and 47 control subjects were included in the analysis. [8] 45 ART subjects and 52 control subjects were included in the analysis. [9] 17 adult ART subjects and 22 adult control subjects were included in the analysis. [10] 50 minor ART subjects and 64 minor control subjects were included in the analysis. Maternal educational level was assessed according to the German educational system: no school leaving qualification (0), lower secondary school leaving certificate (1), intermediate secondary school leaving certificate (2), general qualification for university entrance (3), completed apprenticeship (4), completed university degree (5). Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. Nominal data is presented as n (%). *** $p \leq 0.001$.

Table 2. Vascular Function in the ART and Control Group.

Variable	ART (n = 67)	Control (n = 86)	*p*-Value
SBP (mmHg)	113.64 ± 12.02	113.24 ± 8.96	0.82
DPB (mmHg)	65.00 (59.00–72.00)	63.50 (59.00–71.25)	0.96
PWV (m/s)	4.63 ± 0.55	4.62 ± 0.41	0.88
AAO CS (%) [1]	22.46 ± 6.74	22.42 ± 8.26	0.97
AAO SR (1/s) [2]	4.15 ± 0.98	4.14 ± 1.20	0.94
AAO Dis (mmHg^{-1} × 10^{-3}) [1]	950 ± 325	969 ± 398	0.75
AAO β index [3]	2.47 (1.72–3.72)	2.54 (1.85–3.69)	0.61
rCCA CS (%) [4]	13.71 ± 3.41	14.60 ± 4.68	0.18
rCCA SR (1/s) [4]	3.82 (3.38–4.50)	4.10 (3.23–4.93)	0.13
rCCA Dis (mmHg^{-1} × 10^{-3}) [4]	580 ± 177	628 ± 222	0.16
rCCA β index long axis [5]	3.87 (2.90–5.31)	3.69 (2.62–5.58)	0.54
lCCA CS (%) [4]	14.73 (12.10–17.67)	14.88 (11.08–17.82)	0.67
lCCA SR (1/s) [4]	4.04 ± 1.02	4.00 ± 1.15	0.82
lCCA Dis (mmHg^{-1} × 10^{-3}) [4]	633 (450–727)	599 (448–745)	0.80
lCCA β index long axis [6]	3.26 (2.33–4.32)	3.06 (2.57–4.08)	0.74

ART = assisted reproductive technologies; SBP = systolic blood pressure; DBP = diastolic blood pressure; PWV = pulse wave velocity, AAO = abdominal aorta; CS = peak circumferential strain; SR = peak strain rate; Dis = arterial distensibility; rCCA = right common carotid artery; lCCA = left common carotid artery. [1] 63 ART subjects and 83 control subjects were included in the analysis. [2] 64 ART subjects and 83 control subjects were included in the analysis. [3] 62 ART subjects and 83 control subjects were included in the analysis. [4] 64 ART subjects were included in the analysis. [5] 66 ART subjects were included in the analysis. [6] 66 ART subjects and 85 control subjects were included in the analysis. Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters.

3.3.1. Arterial Stiffness in Children ≥ 10 Years of Age

In total, 38 ART subjects and 55 controls ≥ 10 years of age were included for the sub-analysis. Both groups did not differ significantly in age, gender, bodyweight, body height, BMI and smoking status. Compared to spontaneously conceived peers, birth weight, birth height and gestational age were significantly lower, whereas the number of multiple pregnancies was significantly higher in the ART group. No significant difference in adherence to the Mediterranean Diet was demonstrated between ART subjects and spontaneously conceived peers. ART adults tended to have a lower adherence to the Mediterranean diet compared to controls. Table 3 visualizes data on patients' characteristics in the ART and control group aged ≥ 10 years.

Table 3. Patients' Characteristics in the ART and Control Group Aged ≥ 10 Years.

Variable	ART (n = 38)	Control (n = 55)	*p*-Value
Age (years)	17.06 (12.40–20.66)	16.15 (11.99–21.75)	0.99
Female (n (%))	21 (55.3)	28 (50.9)	0.68
Bodyweight (kg)	55.24 ± 15.19	56.05 ± 13.96	0.79
Body height (cm)	162.77 ± 13.25	166.94 ± 13.10	0.14
BMI (kg/m^2)	20.44 ± 3.28	19.81 ± 3.11	0.35
Weight classification			0.73
Underweight (n (%))	3 (7.9)	6 (10.9)	
Normal weight (n (%))	30 (78.9)	45 (81.8)	
Overweight (n (%))	5 (13.2)	4 (7.3)	
Smoking (n (%))	3 (7.9)	1 (1.8)	0.16
Course of Pregnancy and Birth, Maternal Educational Level			
Birth weight (g) [1]	2995 (2218–3197.50)	3425 (3170–3671.25)	<0.001 ***
Birth height (cm) [2]	50 (48–52)	51 (50–54)	0.004 **
Gestational age (weeks) [3]	38 (34–39)	39 (38–40)	0.012 *
Multiple pregnancy (n (%))	13 (34.2)	2 (3.6)	<0.001 ***
Maternal age at birth (years) [4]	34.03 ± 3.42	32.94 ± 4.20	0.19
Maternal BMI at conception (kg/m^2) [5]	22.49 (20.55–25.26)	21.23 (19.89–23.21)	0.38
Gestational diabetes (n (%)) [6]	1 (3.2)	0 (0)	0.43
Maternal blood pressure during pregnancy ≥ 140/90 mmHg (n (%)) [7]	0 (0)	1 (4.2)	1
Maternal educational level [8]	4 (2–5)	5 (4–5)	0.14
Diet Quality			
MEDAS [9]	5.94 ± 2.51	7.27 ± 1.67	0.05
KIDMED [10]	5.76 ± 2.45	6.27 ± 2.10	0.42

ART = assisted reproductive technologies; BMI = body mass index. [1] 36 ART subjects and 48 con-trol subjects were included in the analysis. [2] 34 ART subjects and 48 control subjects were included in the analysis. [3] 35 ART subjects and 47 control subjects were included in the analysis. [4] 37 ART subjects were included in the analysis. [5] 23 ART subjects and 34 control subjects were included in the analysis. [6] 31 ART subjects and 41 control subjects were included in the analysis. [7] 12 ART subjects and 24 control subjects were included in the analysis. [8] 25 ART subjects and 38 control subjects were included in the analysis. [9] 17 adult ART subjects and 22 adult control subjects were included in the analysis. [10] 21 minor ART subjects and 33 minor control subjects were included in the analysis. Maternal educational level was assessed according to the German educational system: no school leaving qualification (0), lower secondary school leaving certificate (1), intermediate secondary school leaving certificate (2), general qualification for university entrance (3), completed apprenticeship (4), completed university degree (5). Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. Nominal data is presented as n (%). * $p < 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.

Within study participants ≥ 10 years of age, vascular parameters did not show significant differences between both groups. SBP displayed a higher tendency in the ART group compared to the control group but did not reach statistical significance. Table 4 summarizes data on vascular function in the ART and control group aged ≥ 10 years.

Table 4. Vascular Function in the ART and Control Group Aged ≥ 10 Years.

Variable	ART (n = 38)	Control (n = 55)	*p*-Value
SBP (mmHg)	120.18 ± 9.57	116.55 ± 8.05	0.05
DPB (mmHg)	69.79 ± 7.63	67.96 ± 7.95	0.27
PWV (m/s)	4.87 ± 0.41	4.80 ± 0.38	0.41
AAO CS (%) [1]	22.05 ± 7.39	21.87 ± 7.54	0.91
AAO SR (1/s) [1]	4.22 ± 1.04	4.21 ± 1.14	0.98
AAO Dis ($mmHg^{-1} \times 10^{-3}$) [1]	895 ± 338	920 ± 346	0.73
AAO β index [2]	2.74 (1.85–3.89)	2.44 (1.88–3.53)	0.65
rCCA CS (%)	13.39 ± 3.16	13.64 ± 3.82	0.74
rCCA SR (1/s)	3.92 ± 0.86	3.91 ± 0.96	0.98
rCCA Dis ($mmHg^{-1} \times 10^{-3}$)	540 ± 143	572 ± 179	0.36
rCCA β index long axis	3.93 (2.90–5.53)	4.09 (2.71–5.64)	0.86
lCCA CS (%) [3]	14.14 ± 3.97	13.74 ± 4.19	0.64
lCCA SR (1/s) [3]	3.84 ± 1.07	3.72 ± 1.02	0.57
lCCA Dis ($mmHg^{-1} \times 10^{-3}$) [3]	574 ± 183	569 ± 171	0.90
lCCA β index long axis [1]	3.54 (2.56–4.76)	3.37 (2.69–4.40)	0.70

ART = assisted reproductive technologies; SBP = systolic blood pressure; DBP = diastolic blood pressure; AAO = abdominal aorta; CS = peak circumferential strain; SR = peak strain rate; Dis = arterial distensibility; rCCA = right common carotid artery; lCCA = left common carotid artery. [1] 54 control subjects were included in the analysis. [2] 37 ART subjects and 52 control subjects were included in the analysis. [3] 37 ART subjects and 55 control subjects were included in the analysis. Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters.

3.3.2. Correlation Analysis

The influence of age on vascular function was studied for each group by conducting a correlation analysis (Table 5). Observed z-scores (Z_{obs}) ranged between −1.189 and 1.529, suggesting no significant differences between the correlations of both groups (Table 5).

Table 5. Correlation Analysis between Age and Vascular Function in the ART and Control Group.

Variable	ART (n = 67)		Control (n = 86)		Z_{obs}
	r	*p*-Value	r	*p*-Value	
SBP (mmHg)	0.690	<0.001 ***	0.633	<0.001 ***	0.610
DBP (mmHg)	0.642	<0.001 ***	0.510	<0.001 ***	1.195
PWV (m/s)	0.742	<0.001 ***	0.807	<0.001 ***	−0.983
AAO CS (%) [1]	−0.211	0.098	−0.131	0.238	−0.483
AAO SR (1/s) [2]	0.099	0.437	0.056	0.616	0.255
AAO Dis ($mmHg^{-1} \times 10^{-3}$) [1]	−0.368	0.003 **	−0.181	0.102	−1.189
AAO β index [3]	0.232	0.07	−0.026	0.816	1.529
rCCA CS (%) [4]	−0.159	0.209	−0.243	0.024 *	0.519
rCCA SR (1/s) [4]	−0.020	0.874	−0.257	0.017 *	1.440
rCCA Dis ($mmHg^{-1} \times 10^{-3}$) [4]	−0.303	0.015 *	−0.263	0.014 *	−0.258
rCCA β index long axis [5]	0.114	0.361	0.256	0.018	−0.882
lCCA CS (%) [4]	−0.276	0.027 *	−0.308	0.004 **	0.207
lCCA SR (1/s) [4]	−0.256	0.041 *	−0.371	<0.001 ***	0.758
lCCA Dis ($mmHg^{-1} \times 10^{-3}$) [4]	−0.374	0.002 **	−0.407	<0.001 ***	0.231
lCCA β index long axis [6]	0.132	0.292	0.208	0.056	−0.467

ART = assisted reproductive technologies; Z_{obs} = observed z-score; SBP = systolic blood pressure; DBP = diastolic blood pressure; PWV = pulse wave velocity, AAO = abdominal aorta; CS = peak circumferential strain; SR = peak strain rate; Dis = arterial distensibility; rCCA = right common carotid artery; lCCA = left common carotid artery. [1] 63 ART subjects and 83 control subjects were included in the analysis. [2] 64 ART subjects and 83 control subjects were included in the analysis. [3] 62 ART subjects and 83 control subjects were included in the analysis. [4] 64 ART subjects were included in the analysis. [5] 66 ART subjects were included in the analysis. [6] 66 ART subjects and 85 control subjects were included in the analysis. Data is presented as mean ± SD for normally distributed parameters and as median (IQR) for non-normally distributed parameters. * $p < 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.

4. Discussion

67 ART subjects and 86 age- and gender-matched spontaneously conceived peers make this study one of the biggest of its kind. Recently, 2DST has been introduced as a new method to evaluate arterial stiffness [21]. To the best of our knowledge, 2DST has not been applied yet to assess arterial stiffness in the ART offspring. In contrast to previous findings [15,32,33], the present study displayed no significant differences in arterial stiffness, visualized by CS, SR, Dis and stiffness index β of the AAO and the CCA, between ART subjects and spontaneously conceived peers. In addition, oscillometric assessed PWV, SBP and DBP did not differ significantly between both groups.

In the sub-analysis of subjects $\geq$ 10 years of age, no significant differences in the cardiovascular parameters studied were shown between ART subjects and spontaneously conceived peers.

Moreover, the correlation analysis did not reveal a more pronounced alteration of vascular function with age in the studied ART cohort.

4.1. Assisted Reproductive Technologies: A Potential Cardiovascular Risk Factor for the Offspring?

4.1.1. Comparison to Previous Findings

Each year, an increasing number of children are born using ART [34]. With more than 10 million ART children born, their long-term health outcomes deserve special interest [10,34]. This study suggests that vascular function does not differ significantly between ART subjects and spontaneously conceived peers. To evaluate whether vascular aging is more pronounced in the ART offspring, subjects at different ages (children, adolescents, young adults) were intentionally included. Interestingly, when analyzing study participants $\geq$ 10 years of age, parameters of arterial stiffness remained unchanged between both groups. In addition, no significant differences between the correlations of age and the cardiovascular parameters studied were revealed between both groups. Hence, our study supports recent findings of normal vascular function in ART subjects [19,35].

Halliday et al. demonstrated in a cohort of 193 ART subjects who were matched to 86 spontaneously conceived peers (mean age: 27.5 $\pm$ 2.8 years vs. 27.6 $\pm$ 2.6 years) no significantly elevated vascular or cardiometabolic risk profile [19]. Outcome measures were parameters of vascular structure, such as carotid artery intima-media thickness, pulse wave velocity and blood pressure [19]. The study conducted by Halliday et al. reinforces the perception that ART does not affect the vascular health of its offspring [19]. These findings are supported by a cohort study including data of 122,429 ART and 7,547,685 naturally conceived children from Sweden, Finland, Norway and Denmark [36]. The study conducted by Norrman et al. could not display a significantly increased risk for CVD (e.g., ischemic heart disease, cardiomyopathy, heart failure, cerebrovascular disease) and type 2 diabetes in ART subjects [36]. However, a significantly elevated risk for obesity was shown for the ART offspring [36]. The large sample size and the prior adjusting for several confounders (e.g., maternal CVD, obesity, diabetes) reinforce the demonstrated results of the current study [36]. However, the short time of follow-up and the relatively young age of the studied populations might underestimate the impact of ART on the offspring's cardiovascular system as subjects could develop increased cardiovascular morbidity only later in life [36].

In contrast, multiple studies support the hypothesis that the ART offspring might be exposed to greater health risks compared to naturally conceived peers [11,15,18,34,37,38]. Various short-term consequences, including preterm birth, low birth weight and higher perinatal mortality were demonstrated [15,37]. The available data on long-term consequences is sparse, but neurodevelopmental deficits, abnormalities in glucose metabolism and the early development of metabolic syndrome are named as potential adverse health outcomes [11,15,37]. In the literature, cardiovascular remodeling within the ART offspring is assumed [16,18,39]. A well-known Swiss study reported generalized endothelial dysfunction, increased intima-media thickness and elevated arterial stiffness in a cohort of 65 ART singletons compared to 57 spontaneously conceived controls [17,33]. Five years after the initial examination, the premature vascular aging persisted in the ART cohort [32]. A review and meta-analysis by Guo et al. published in 2017, investigated the cardiovascular function of 2112 IVF/ICSI subjects and 4096 spontaneously conceived peers [18]. Interestingly, the authors observed a significantly increased blood pressure, significantly thicker vessel walls and a suboptimal cardiac diastolic function in the ART cohort [18]. The analysis was limited by the number of included studies and the relatively young age of study participants [18].

4.1.2. Pathophysiological Considerations

ART were introduced in 1978 and have made substantial progress in the last 40 years [18,40]. IVF, the primary implemented technique, and ICSI, introduced several years later, are nowadays the most frequently used techniques [15]. ART undergo constant improvements of treatment protocols, culture conditions, quality controls as well as efficiency in fertilization and pregnancy rates leading to higher success rates [18,40,41]. As a result, a decrease in adverse perinatal outcomes including preterm birth and low birth weight was noticed within the ART offspring [42]. Moreover, it was observed that the rate of multiple births dramatically declined over the last decades of using ART [42]. As these factors are known risks for prematurity and increased perinatal mortality, its reduction might be one possible explanation for an overall improvement of the perinatal ART outcome [42]. Additionally, the introduction of cryopreservation as an alternative to fresh embryo transfer might have led to a reduction of prematurity and to an elevation of mean birth weight [43]. Nowadays, ICSI treatments represent approximately 70% of all ART worldwide [10]. Recent studies could not determine a superiority in postfertilization reproductive outcome compared to IVF [44], however, an overall lower preterm birth rate was detected within the ICSI treatment cohort [45]. Interestingly, birth weight, birth height and gestational age were significantly lower in the ART cohort of the current study. Low birth weight and prematurity are associated with several health conditions later in life, such as elevated arterial stiffness and, therefore, an increased risk of CVD development [46–48]. Hence, the demonstrated ART improvements and the reduction of associated short-term consequences might contribute to a better long-term ART outcome including lower cardiovascular morbidity and mortality.

The "developmental origins of adult disease" hypothesis is often used to link adverse environmental influences during early human development, such as the ART procedure itself, to increased cardiovascular risk later in life [38]. As the cardiovascular system is one of the first to be matured in the embryonic development, it might be easily affected by adverse environmental influences [34]. During the ART procedure the gametes and embryos are exposed to excessive oxidative stress levels potentially caused by a lack of natural antioxidant systems and other stimuli (e.g., fluctuation in temperature, pH, oxygen concentration) facilitating oxidative stress production [34]. As a result, potential epigenetic modifications in the offspring's DNA could cause cardiovascular alterations later in life [34]. Within the last years, the embryo culture environment as well as the media composition was further optimized leading to a reduction of oxidative stress levels and DNA methylation [49,50]. Presumably, this optimization could have positively influenced the health outcome of the ART offspring.

Fertility is negatively affected by advanced age and pre-existing CVD risk factors [34,51–53]. Animal, human and epidemiological studies demonstrated that advanced maternal age might be associated with lower long-term cardiovascular health of the offspring. Moreover, adult offspring of parents with CVD (e.g., coronary artery disease, cerebrovascular disease, peripheral artery disease) display a higher prevalence of hypercholesteremia and hypertension compared to the general population [14]. Advanced maternal age, chronic hypertension and the use of ART are known risk factors for preeclampsia [54]. Preeclampsia itself, is associated with negative health effects for the fetus leading to increased cardiovascular risk later in life [55]. Presumably, couples with increased age and cardiovascular morbidity might require ART more frequently. As ART procedures undergo continuous development, these techniques might be accessible to an even more morbid cohort in the future [42].

4.2. Strengths and Limitations

4.2.1. Study Design

This study was a single center study within Germany. The sample size of this study can be considered as one of the biggest ever reported in the literature. As this study used novel parameters to assess arterial stiffness, a prior power analysis was not feasible. However, a study conducted by Scherrer et al., displayed significant differences in conventional vascular parameters in a cohort of 65 ART subjects and 57 spontaneously conceived peers [33]. Therefore, we aimed for a similar sample size for the present study.

For this study, adverse perinatal conditions (e.g., preterm birth, multiple pregnancy) were purposely not defined as exclusion criteria for study participation. A prior exclusion of such participants was thought to positively influence the "real" cardiovascular risk profile of the studied ART population and to substantially limit the sample size of this single center study. Hence, for a more detailed cardiovascular risk stratification of the ART cohort (e.g., preterm birth, multiple pregnancy, single ART treatments), prospective multi-centric studies with a longitudinal study design and an even greater sample size are required in the future.

ART procedures undergo continuous development [18,40,41]. Hence, the potential impact of new ART methodologies on the offspring's cardiovascular function needs to be closely monitored in future studies.

GIFT was considered as a conventional form of ART in this study. Compared to IVF or ICSI, GIFT does not imply in vitro cultivation as fertilization occurs in the natural milieu of the fallopian tubes.

As infertility is associated with increased cardiovascular morbidity [17,37], the potential inheritance of parental cardiovascular risk factors needs to be addressed in future ART studies.

In this study, data on pregnancy and birth was assessed retrospectively by screening clinical records and by questioning both parents. However, a loss of information was inevitable in some study participants as clinical records were either "lost" or incompletely filled out by prior healthcare professionals.

The present study did not take psychosocial factors into consideration as relevant cardiovascular risk factors. Seeland et al. suggests vascular ageing to be associated with mood disorders, personality traits and social isolation [13].

It is known that certain lifestyle habits might have an impact on vascular function. In the current study, neither smoking nor diet quality did significantly differ between both groups. However, ART adults tended to have a lower adherence to the Mediterranean diet.

4.2.2. Methodology

For 2DST, the use of a sector array transducer was required by the software. Compared to a linear transducer this might have led to a lower image resolution potentially influencing the tracking of speckles.

To the best of our knowledge, 2DST of the AAO and the CCA has not been validated yet. In addition, pediatric reference values for 2DST assessed arterial stiffness parameters do not exist yet. However, multiple studies suggest that 2DST can be a useful tool for the non-invasive assessment of arterial stiffness compared to the current gold standard of carotid–femoral pulse wave velocity [22,56,57]. Moreover, 2DST might facilitate the regional evaluation of central arterial stiffness compared to conventional methods that assess "global" arterial stiffness peripherally [58]. Nonetheless, it needs to be pointed out that a regional estimation of arterial stiffness might be accompanied by lower accuracy compared to a global assessment [58]. Therefore, this study assessed arterial stiffness additionally by measuring PWV via an oscillometric device. In addition, 2DST tended to overestimate strain values in an experimental study [58].

Further, the potential influence of extrinsic mechanical factors (e.g., chest wall conformation) on arterial elastance and ventricular–arterial coupling needs to be addressed and investigated in further studies [59,60].

As previously shown, 2DST of the AAO displays a relatively high intra-and inter-observer variability [61]. To reduce intraobserver variability in this study, an average of three measurements was calculated to enhance data validity. To minimize interobserver variability, one investigator conducted acquisition and offline analysis of the sonographic images. As the quality of 2DST is highly dependent on the sonographic window, imprecise tracking of speckles might be present in subjects with excess weight [61].

5. Conclusions

The present study displayed no significant differences in arterial stiffness between ART subjects and spontaneously conceived peers, visualized by CS, SR, Dis and stiffness index β of the AAO and the CCA as well as PWV. In addition, the results of this study suggest that arterial stiffness does not elevate more profoundly in ART subjects with increasing age compared to spontaneously conceived peers. In the future, prospective multi-centric studies with a longitudinal study design and an even greater sample size are required for a more detailed cardiovascular risk stratification of the ART cohort.

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Institutional Review Board Statement: The study was performed in accordance with the ethical standards of the Declaration of Helsinki. The Ethics Committee of the Medical Faculty of the Ludwig Maximilians University Munich (Munich, Germany) approved this study (protocol code: 20-0844, date of approval: 27 December 2020).

Informed Consent Statement: All participants gave their written informed consent to participate in the present study. For minor study participants, prior written informed consent was additionally given from parents or legal guardians.

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Übereinstimmungserklärung

LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Erklärung zur Übereinstimmung der gebundenen Ausgabe der Dissertation mit der elektronischen Fassung

Langer, Magdalena Silvia

Name, Vorname

Hiermit erkläre ich, dass die elektronische Version der eingereichten Dissertation mit dem Titel:

Prospektive Evaluierung der vaskulären Morbidität von Nachkommen, die durch assistierte Reproduktionstechniken gezeugt wurden

in Inhalt und Formatierung mit den gedruckten und gebundenen Exemplaren übereinstimmt.

München, den 07.08.2025

Ort, Datum

Magdalena Silvia Langer

Unterschrift Magdalena Silvia Langer

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