Aus dem CharitéCentrum 17 für Frauen-, Kinder- und Jugendmedizin

mit Perinatalmedizin und Humangenetik

Klinik für Geburtsmedizin

Campus Virchow Klinikum/Campus Charité Mitte

Direktor: Prof. Dr. med. W. Henrich

Habilitationsschrift

Personalisierte und risikoorientierte Betreuung von Schwangeren in der Geburtsmedizin und Pränataldiagnostik

zur Erlangung der Lehrbefähigung

für das Fach Frauenheilkunde und Geburtshilfe

vorgelegt dem Fakultätsrat der Medizinische Fakultät

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1. Einleitung

1.1. Die Ära der modernen Geburtsmedizin

Die Geburtsmedizin hat in den letzten Jahrzehnten eine bemerkenswerte Transformation erlebt, die von wegweisenden Fortschritten in der pränatalen Diagnostik und einer verstärkten Ausrichtung auf die personalisierte und risikoorientierte Betreuung von Schwangeren geprägt ist. Diese Entwicklung schafft die Grundlagen für eine qualitativ hochwertige, individualisierte Versorgung von werdenden Müttern und ihren ungeborenen Kindern. Diese Arbeit beleuchtet einige relevante Aspekte der personalisierten und risikoadaptierten Betreuung von Schwangeren. Fünf Publikationen zum Thema: Gewichtszunahme in der Schwangerschaft, Gestationsdiabetes, Zervixreifung nach Kaiserschnitt sowie genetische Diagnostik bei fetalen Fehlbildungen der ableitenden Harnwege und die Beurteilung der fetalen Herzsachse bei Kindern mit Herzfehler werden genannt. Die Diskussion gibt einen Ausblick über die rasante Evolution in der künstlichen Intelligenz und genetischen Diagnostik in der Pränataldiagnostik.

1.2. Die Schwangerenvorsorge zur frühzeitigen Risikofeststellung

In Deutschland hat jede schwangere Frau als Mitglied einer gesetzlichen Krankenversicherung Anspruch auf eine regelmäßige ärztliche Untersuchung und Beratung im Rahmen der Mutterschaftsrichtlinien. Ziel der Vorsorge ist die Erkennung von Risikoschwangerschaften und deren adäquate Überwachung. Es werden Aspekte wie Infektionen, Krebsvorsorge, Erkrankungen, fetales Wachstum sowie mütterliche Faktoren inklusive Vitalparametern erhoben und aufgezeichnet, um frühzeitig auf mögliche Risiken reagieren zu können und die Schwangere entsprechend personalisiert zu betreuen (1). Die vorgesehenen Untersuchungen und Beratungen sind im Rahmen der Mutterschaftsrichtlinien des Gemeinsamen Bundesausschusses (G-BA) geregelt. Es werden Routineuntersuchungen sowie zusätzliche Untersuchungen bei einem bestehenden Risiko angeboten. Die Schwangere erhält einen Mutterpass, in dem die Angaben zum Gesundheitszustand, zum Verlauf sowie zu möglichen Komplikationen notiert werden.

Zu den Früherkennungsuntersuchungen gehören Ultraschall (Screeninguntersuchungen), die Tests auf HIV, Gestationsdiabetes (GDM) und fetalen Rhesusfaktor, der nichtinvasive Pränataltest auf Trisomie 13, 18 und 21 sowie weitere Analysen (1, 2). Laut G-BA sind drei sonographische Screeninguntersuchungen vorgesehen. Das erste Screening erfolgt zwischen Schwangerschaftswoche (SSW) 8 + 0 und 11 + 6 und hat vor allem den Zweck, den Sitz der Schwangerschaft zu beurteilen sowie gegebenenfalls vorhandene Mehrlinge festzustellen und einzuordnen. Die detaillierte Screeninguntersuchung ist im zweiten Trimenon zwischen SSW 18 + 0 und 21 + 6 vorgesehen. Dabei werden mehrere Organsysteme detailliert untersucht mit dem Ziel, Fehlbildungen auszuschließen (so genanntes IIb-Screening). Das dritte Screening wird zwischen SSW 28 + 0 und 31 + 6 durchgeführt und dient vor allem der Einschätzung des kindlichen Wachstums und der Entwicklung.

1.3. Pränataldiagnostik – angebotene Untersuchungen und mögliche weiterführende Diagnostik

Zusätzlich zur Schwangerschaftsvorsorge werden folgende Screeninguntersuchungen in der Pränataldiagnostik angeboten: das Ersttrimesterscreening (ETS) und die Feindiagnostik (FD). Das ETS sowie die FD werden unter optimalen Bedingungen nach einem standardisierten Protokoll mit spezifischen Qualitätsanforderungen von ExpertInnen durchgeführt (3-6).

Das ETS findet zwischen SSW 11 + 0 und 13 + 6 statt und ist eine Screeninguntersuchung für fetale Fehlbildungen, Trisomien und Präeklampsie (4, 6). Zahlreiche fetale Strukturen, wie zum Beispiel das kardiovaskuläre System, können bereits im ETS beurteilt werden. Das Präeklampsie-Risiko wird im ETS aus multiplen Faktoren und Befunden berechnet. Dabei wird die mütterliche Anamnese sowie der aktuelle Blutdruck und die uterine Perfusion eingeschlossen zur Bewertung. Die Gabe von 150 mg Aspirin täglich vor der 16. SSW kann die Inzidenz einer Präeklampsie vor der 37. SSW um 62 % reduzieren (7). Zusätzlich ist der nichtinvasive Pränataltest (NIPT) verfügbar (2). Der NIPT analysiert cfDNA (cell free DNA) aus dem maternalen Blut (8). Hierbei werden plazentare DNA-Fragmente auf das Vorliegen einer Trisomie 21, 13 bzw. 18 untersucht. Seit Juli 2022 ist der NIPT für jede Schwangere als Kassenleistung verfügbar, sobald „eine Frau gemeinsam mit ihrer Ärztin oder ihrem Arzt zu der Überzeugung kommt, dass der Test in ihrer persönlichen Situation notwendig ist“ (2). Die

Kombination des NIPT und des ETS hat in einer prospektiven Analyse eine Sensitivität von 90 % bei einer Spezifität von 97 % hinsichtlich der Detektion einer Trisomie 21 gezeigt (9). Die International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) empfiehlt die sequenzielle Anwendung des NIPT als Zweitlinien-Screening nach dem ETS (10, 11). Die Detektionsrate für fetale Anomalien im ETS liegt bei 46,1 bis 47,8 % (12, 13). Die Anwendung eines standardisierten Protokolls mit Qualitätsanforderungen wurde als relevanter Einflussfaktor der Detektionsrate identifiziert *(p*-Wert < 0,0001) (5, 6, 13). Eine aktuelle Metaanalyse konnte zeigen, dass insgesamt 63,67 % aller schweren Herzfehler bereits im ersten Trimester in einem Niedrigrisikokollektiv detektiert werden können (1445 CHD, Prävalenz 0,41 % [95 % CI, 0,39 bis 0,43 %], 767 identifiziert im ETS) (13).

Die FD wird als differenzierter Ultraschall zwischen SSW 18 + 0 und 21 + 6 angeboten und dient der Untersuchung auf fetale Erkrankungen und Entwicklungsstörungen (3). Die Identifikation fetaler Fehlbildungen im zweiten Trimester wird in der Literatur mit unterschiedlichen Zahlen zwischen 17 und 85 % angegeben (14, 15). Eine retrospektive Untersuchung von 2017 hat 10414 Neugeborene untersucht, dabei hatten 243 Kinder eine Fehlbildung mit einer Prävalenz von 2,3 %. 107 aller Fehlbildungen konnten pränatal diagnostiziert werden, mit einer Detektionsrate von 44,0 % (16). Aktuell läuft eine Cochrane-Analyse zum Thema Detektionsrate der Pränataldiagnostik im zweiten Trimester (17).

Beim Verdacht auf eine fetale Fehlbildung oder ein Syndrom werden die Eltern bezüglich möglicher weiterer Diagnostik beraten. Es können verschiedene weiterführende Untersuchungen durchgeführt werden, je nach Befund und Wunsch der Schwangeren: GDM-Screening, Infektionsserologie, genetische Untersuchungen (invasive und nichtinvasive) sowie andere spezifische Analysen (18).

1.3.1. Pränataldiagnostik – Häufigkeit von fetalen Fehlbildungen

Am Anfang der Untersuchung steht die Frage der Eltern, ob ihr Kind gesund sein wird. Es wird vermutet, dass in 2 bis 4 % aller Schwangerschaften fetale Anomalien vorliegen (19-21). Eine Analyse hat die Frequenz von angeborenen Fehlbildungen in Utah, USA von 2005 bis 2009 untersucht (20). Unter 270 878 Geburten wurden 5504 Fehlbildungen identifiziert, was 2,03 % entspricht (Abbildung 1). In 79,8 % der Fälle fanden sich fetale Malformationen

aufgrund unbekannter Ursachen. Bei 15,3 % konnte eine chromosomale Störung festgestellt werden. Insgesamt 7 % der Kinder waren von einer Trisomie 21 betroffen. Bei 3,8 % der angeborenen Fehlbildungen konnte eine monogene Erkrankung diagnostiziert werden. In 0,8 % der Fälle fanden sich Teratogene als Ursache und bei 0,3 % konnte die fetale Fehlbildung durch eine Mehrlingsanlage erklärt werden. Die Untersuchung zeigt, dass strukturelle Fehlbildungen – durch verschiedene Ätiologien bedingt – in dieser Kohorte häufiger sind als Trisomien (94,7 % vs. 15,3 %).

Es lässt sich diskutierten, dass heute der Anteil der Anomalien aufgrund unbekannter Ursachen geringer ist und dafür der Anteil monogener Erkrankungen größer, da sich ein enormer Wissenszugewinn in der genetischen Diagnostik vollzogen hat und seit der Studie von Feldkamp *et al.* zahlreiche seltene genetische Erkrankungen pränatal identifiziert wurden (22).

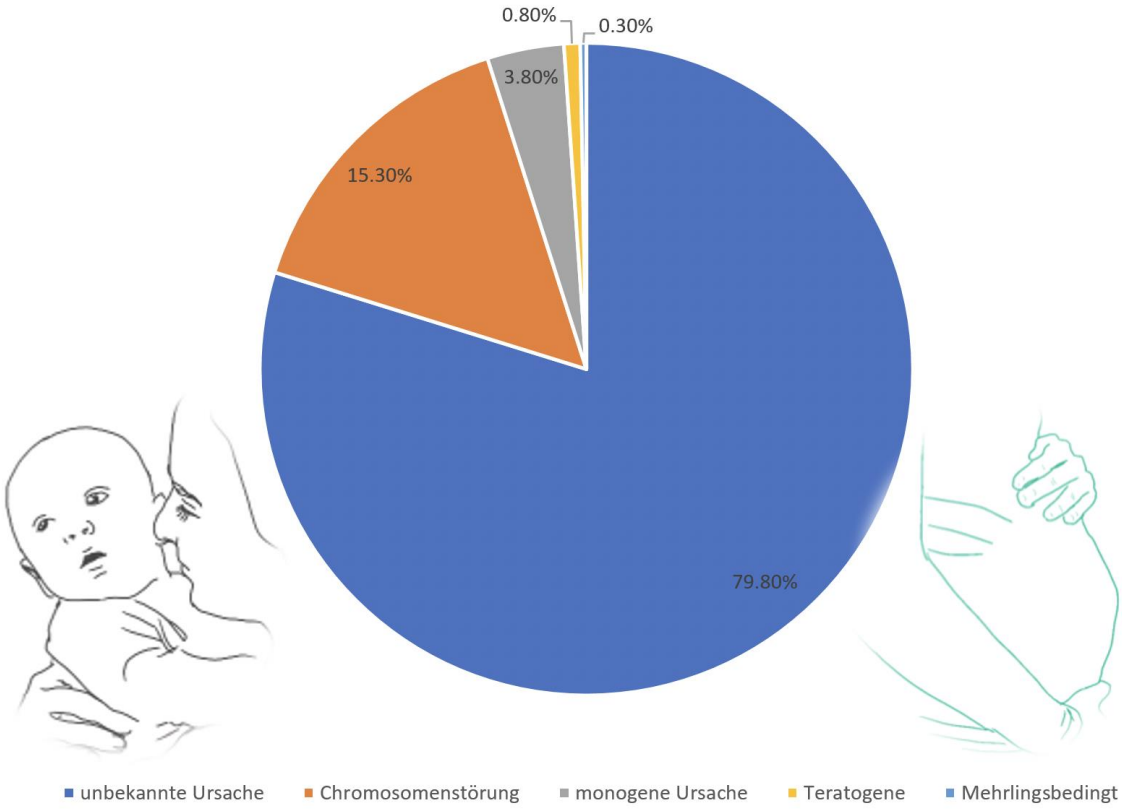

Abbildung 1: *Häufigkeit von angeborenen Fehlbildungen in einer Kohorte von 270 878 Geburten in den USA (Grafik von der Autorin nach (20)). In 79,8 % der Fälle fanden sich fetale Malformationen aufgrund unbekannter Ursachen.*

Zur weiterführenden genetischen Analyse stehen verschiedene Untersuchungen zur Verfügung (23). Prinzipiell kann nach invasiven und nichtinvasiven Methoden unterschieden werden (Abbildung 2). Der NIPT ist unter bestimmten Bedingungen als Kassenleistung verfügbar (2). Durch den NIPT erfolgt die Analyse von plazentaren DNA-Fragmenten, so genannter cfDNA, aus dem maternalen Blut. Die gängigste Untersuchung bezieht sich auf das Vorliegen einer Trisomie 21, 13 bzw. 18. Die Entwicklungen gehen in Richtung Erweiterung des NIPT auf das Screening von anderen seltenen Aneuploidien (seltene autosomale Trisomien/Rate Autosomal Trisomies = RAT, Geschlechtschromosomen Aneuploidien/Sex Chromosome Aneuploidy = SCA) und Strukturvarianten (Copy Number Variant = CNV) sowie monogenen Erkrankungen (11, 24, 25). Eine Untersuchung, bei der Frauen parallel zur invasiven Diagnostik einen erweiterten NIPT erhielten, zeigte, dass bei 63,86 % der Fälle das Ergebnis der invasiven Diagnostik per NIPT bestätigt werden konnte. Die Autoren weisen darauf hin, dass die Detektionsrate eng mit der Größe der CNV zusammenhängt. Bei ≥5 Megabasen war die Detektionsrate sehr gut. Lag die Größe der betroffenen CNV jedoch darunter, wurde diese nicht durch den NIPT festgestellt (26).

Als invasive Diagnostik kann je nach Zeitpunkt in der Schwangerschaft die Chorionzottenbiopsie bzw. Amniozentese durchgeführt werden, bei der plazentare bzw. kindliche Zellen analysiert werden (Abbildung 2) (23). Seltener und nur bei spezifischen Indikationen erfolgt die Cordozentese (Punktion der Nabelschnur), die Plazentapunktion oder die Punktion des Fetus. Bei Verdacht auf eine fetale Aneuploidie wird initial der fetale Karyotyp bestimmt. Besteht der Hinweis auf eine chromosomale Strukturvariante, im Sinne einer Mikrodeletion oder -duplikation (CNV), empfiehlt sich die Durchführung eines Microarrays (27). Bei Verdacht auf eine monogene Erkrankung bzw. ein komplexes Syndrom wird die Trioexom-Analyse nach genetischer Beratung angeboten (28, 29). Die Exom-Sequenzierung untersucht ausschließlich die Exome von kodierenden Regionen, die ca. 1,5 % der menschlichen DNA ausmachen. Die Trioexom-Analyse ist im Gegensatz zur Genomsequenzierung deutlich kosteneffektiver und schneller (30). In den letzten Jahren gewann die Trioexom-Analyse zunehmend an Bedeutung.

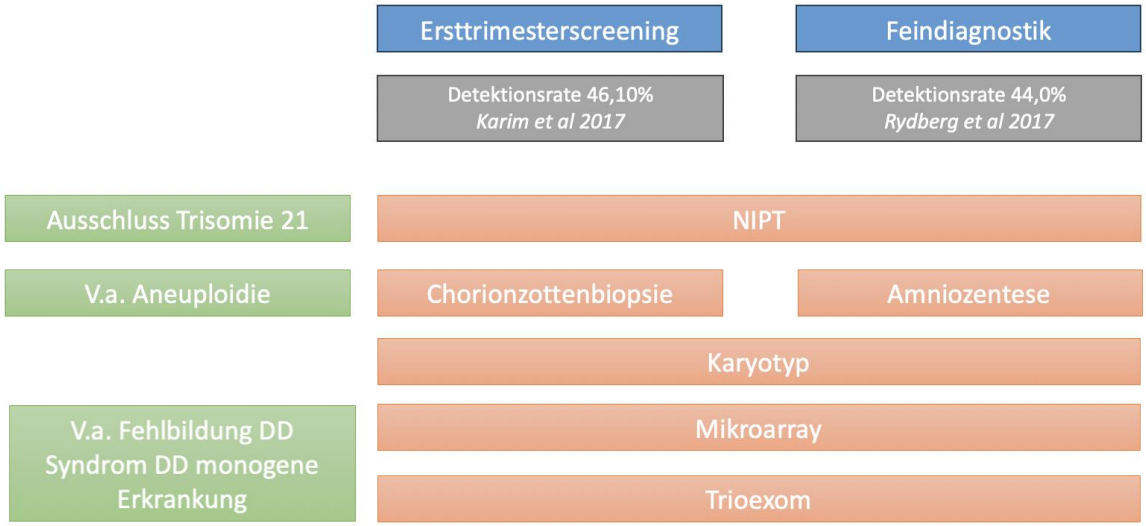

Abbildung 2: *Ablauf der angebotenen pränatalen Untersuchungen und mögliche diagnostische Prozeduren. NIPT = nichtinvasiver pränataler Test (13, 16, 31). Die genetische Diagnostik erfolgt stufenweise und je nach Schwangerschaftsalter und Verdacht sowie nach Wunsch der Patientin (Grafik von der Autorin).*

1.4. Herausforderungen durch den Wandel des Patientinnenkollektivs

Insgesamt haben sich nicht nur die Pränataldiagnostik und die Geburtsmedizin gewandelt, sondern auch die demographische Struktur und somit das Risikoprofil von Frauen in ihrer reproduktiven Phase. Eine Untersuchung von Schwangeren der letzten 20 Jahre im Bundesland Schleswig-Holstein ergab, dass das durchschnittliche Gewicht im Laufe des Beobachtungszeitraums von 67,6 auf 72,0 kg gestiegen ist und der Anteil von adipösen Frauen sich von 9,4 auf 19,2 % erhöhte (32). Dies entspricht auch der Bevölkerungsentwicklung in Deutschland und der Welt: Es zeigt sich ein zunehmender Anteil an Frauen mit Übergewicht oder Adipositas (Abbildung 3) (33-35).

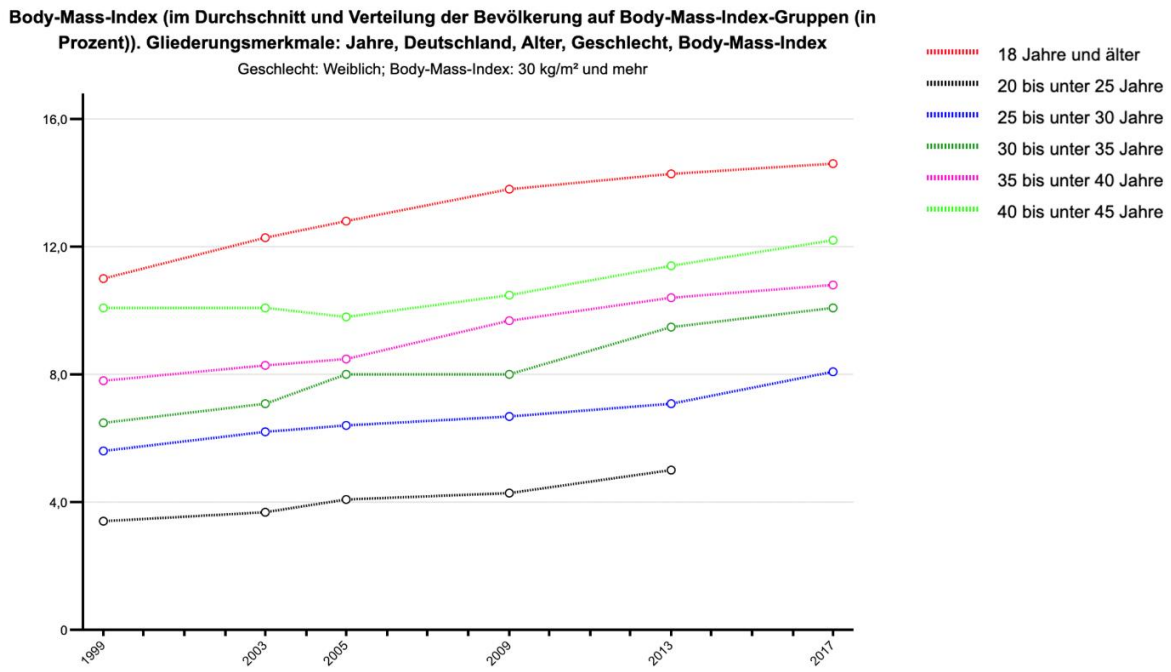

Abbildung 3: *Gewichtsentwicklung in Deutschland bei Frauen im Zeitraum von 1997 bis 2017. Hier dargestellt ist der Anteil von Frauen mit einem BMI von ≥30. Insgesamt ist ein deutlicher Aufwärtstrend zu verzeichnen (33).*

Im Zuge dieser Veränderungen sind immer mehr Frauen vor oder zu Beginn der Schwangerschaft übergewichtig oder adipös (36, 37). Das perikonzeptionelle Übergewicht stellt eine zusätzliche Herausforderung für die Geburtsmedizin dar und kann das Risiko für Komplikationen während der Schwangerschaft und der Geburt erhöhen (34, 38). Es steht in direktem Zusammenhang mit kurzfristigen und langfristigen mütterlichen und kindlichen Komplikationen und ist aus diesem Grund ein ernstzunehmendes Problem (35). Maternales Übergewicht erschwert zusätzlich durch die adipösen Bauchdecken die Detektion von fetalen Fehlbildungen (34). Es bestehen Empfehlungen zur Gewichtszunahme in der Schwangerschaft. Daher ist die personalisierte Betreuung und Risikoeinschätzung für Frauen mit Übergewicht oder Adipositas von entscheidender Bedeutung.

Zusätzlich zur Gewichtsproblematik können weitere Faktoren das Risikoprofil Schwangerer beeinflussen. Das höhere mütterliche Alter (Advanced Maternal Age) bezieht sich auf Schwangerschaften bei Frauen über 35 Jahre (39). In den meisten Ländern liegt das durchschnittliche Alter der Mutter bei der Geburt über 30 Jahre (Abbildung 4). Eine Analyse der Zahlen von 1970 und 2000 im Vergleich zum Jahr 2021 zeigt weltweit einen Trend zu einem fortgeschrittenen mütterlichen Alter bei der Geburt (40). In Deutschland waren Frauen

bei der Geburt ihres ersten Kindes im Jahr 2010 noch durchschnittlich 29,0 Jahre alt, 2022 lag diese Zahl bei 30,2 Jahren (41). Während es für viele Frauen heute üblich ist, ihre Kinder in einem späteren Lebensabschnitt zu bekommen, sind mit dieser Entscheidung bestimmte Risiken verbunden.

Fortgeschrittenes mütterliches Alter geht oft mit einem erhöhten Risiko für Komorbiditäten einher, wie arteriellen Hypertonus, Präeklampsie und GDM, und ist mit einem ungünstigen geburtshilflichen und perinatalen Outcome assoziiert (42-44). Eine große Metaanalyse, die 31 090 631 Frauen untersucht hat, ergab eine Assoziation mit dem Risiko für Totgeburt, Entbindung per Kaiserschnitt und mütterliche Mortalität bei erhöhtem mütterlichen Alter (43). Eine personalisierte Betreuung und Risikoeinschätzung für Frauen mit Advanced Maternal Age ist essentiell, um die assoziierten potentiellen Komplikationen zu adressieren und eine optimale Schwangerschaftsbetreuung und Geburt zu ermöglichen.

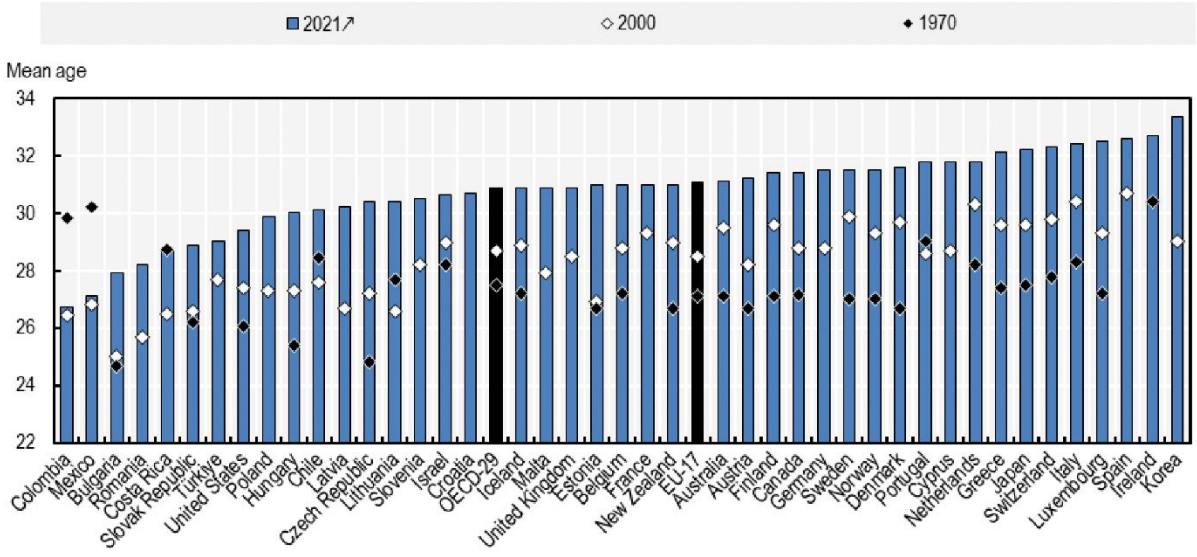

Abbildung 4: *Durchschnittliches Alter der Mutter bei der Geburt in den OECD Ländern 2021, 2000 und 1970 (40). In den meisten Ländern liegt das durchschnittliche Alter bei 30 Jahren. Weltweit ergibt sich für die meisten Länder zwischen 1970 und 2021 ein Aufwärtstrend.*

1.5. Risikofaktor Gewichtszunahme in der Schwangerschaft

Die Gewichtszunahme in der Schwangerschaft ist ein wichtiger und natürlicher Aspekt der körperlichen Veränderungen, die während der Gestationszeit auftreten. Allerdings kann eine unangemessene oder übermäßige Gewichtszunahme Risiken sowohl für die Mutter als auch

für den Fetus mit sich bringen. Die Gewichtskontrolle ist somit ein bedeutender Faktor in der pränatalen Betreuung.

Die empfohlene Gewichtszunahme während der Schwangerschaft variiert je nach dem Ausgangsgewicht der Mutter. Die aktuellen Empfehlungen zur Gewichtszunahme haben ihre Grundlage in den IOM-Guidelines (Institute of Medicine) und basieren auf dem präkonzeptionellen BMI der Mutter (38, 45) (Tabelle 1). Die Empfehlungen sind also für jede Schwangere personalisiert.

Tabelle 1: *Empfehlung bezogen auf die maternale Gewichtszunahme je nach präkonzeptionellem BMI der Mutter (45). BMI = Body Mass Index. ET = errechneter Termin.*

Präkonzeptioneller BMI	**BMI (kg/m^2)**	**Empfohlene Gewichtszunahme gesamt am ET (kg)**	**Empfohlene Gewichtszunahme im 2. und 3. Trimester (kg/SSW)**
Untergewicht	<18.5	12-18	0.45-0.58
Normales Gewicht	18.5-24.9	11.5-16	0.36-0.45
Übergewicht	25.0-29.9	7-11.5	0.22-0.32
Adipositas	≥30.0	5-9	0.18-0.27

In der Regel wird empfohlen, dass Frauen mit einem normalen Gewicht während der Schwangerschaft etwa 11,5 bis 16 kg bis zum Entbindungstermin zunehmen, wogegen Frauen mit Übergewicht oder Adipositas weniger zunehmen sollten (Tabelle 1). Aktuelle Daten weisen darauf hin, dass Frauen mit ausgeprägter Adipositas besonders beraten werden sollten und dass dort die Gewichtszunahme noch geringer sein sollte (46).

Eine übermäßige Gewichtszunahme in der Schwangerschaft ist mit einem erhöhten Risiko für Schwangerschaftskomplikationen wie GDM, arteriellen Hypertonus, Präeklampsie und geburtshilfliche Komplikationen (Geburt per Kaiserschnitt) assoziiert (47, 48). Der maternale Hyperinsulinismus mit Insulinresistenz und oxidativem Stress verursacht eine plazentare Dysfunktion (49). In einer Metanalyse zeigte sich, dass 47 % aller Frauen mehr Gewicht zunehmen als empfohlen (47). Eine ausgeprägte Gewichtszunahme kann ebenfalls

langfristige Auswirkungen auf die Mutter haben (50, 51). Bei Neugeborenen, deren Mütter in der Schwangerschaft zu viel Gewicht zugenommen haben, besteht ein erhöhtes Risiko für Makrosomie/LGA (Large for Gestational Age), für Atemprobleme, für die Entwicklung von Übergewicht und kardiovaskulären Erkrankungen sowie den damit verbundenen Gesundheitsproblemen im späteren Leben (47, 52-54).

Die individuelle und angepasste Überwachung der Gewichtszunahme ist ein relevanter Bestandteil der pränatalen Betreuung. Die Kontrolle der Gewichtszunahme im Laufe der Schwangerschaft ist essentiell, um sicherzustellen, dass sie im gesunden Rahmen bleibt. Auf Basis der bisherigen Forschungslage ist noch nicht eindeutig abzuleiten, welche Maßnahmen ergriffen werden sollen, wenn die Gewichtszunahme zu hoch ist. Es gibt Untersuchungen zu Interventionen durch Ernährungs- und Bewegungsempfehlungen, die eine gesunde Gewichtszunahme fördern (55, 56). Die personalisierte präkonzeptionelle Beratung und ggf. Interventionen bei bereits bestehendem Übergewicht oder Adipositas können helfen, diesen vielschichtigen Komplikationen entgegenzuwirken (55, 57-59).

1.6. Diabetes mellitus Typ 1, 2 und Gestationsdiabetes

Gewichtszunahme, mütterliches Alter stehen in direktem Zusammenhang mit der Entwicklung eines Gestionsdiabetes. Diabetes mellitus ist eine komplexe Gruppe von Stoffwechselerkrankungen, die unter anderem durch eine Hyperglykämie gekennzeichnet sind. Jede der bekannten Diabetes-mellitus-Typen hat einzigartige Merkmale und Auswirkungen auf die Gesundheit und bedarf einer personalisierten Betreuung. Für das Jahr 2021 konnte im Bericht des Instituts für Qualität und Transparenz im Gesundheitswesen (IQTiG) ein Anteil von Schwangeren mit Diabetes mellitus Typ 1 oder Typ 2 von 1,05 % (7954) sowie mit GDM von 9,98 % (59 581) aufgezeichnet werden (von 758 016 Datensätzen) (60). Eine genaue Differenzierung zwischen Diabetes mellitus Typ 1 und 2 ist aufgrund der vorliegenden Daten nicht möglich. Ein Diabetes mellitus in der Schwangerschaft ist mit unterschiedlichen perinatalen Komplikationen assoziiert (61). Unter anderen sind ein erhöhtes Frühgeburtsrisiko, eine erhöhte Rate an Fehlbildungen, fetale Makrosomie, neonatale Atemstörungen und Hypoglykämien sowie komplexe Langzeitfolgen zu verzeichnen (62-64).

Der Diabetes mellitus Typ 1 und Typ 2 zeichnet sich vor allem durch Hyperglykämien aus, die entweder aufgrund eines (absoluten) Insulinmangels und/oder einer Insulinresistenz bestehen (61). Der HbA1c-Wert kann zeigen, wie ausgeprägt die Hyperglykämie in den letzten drei Monaten war, und korreliert mit dem Risiko für fetale Fehlbildungen (63, 65, 66). Ein hoher HbA1c-Wert während der Schwangerschaft ist ein Hinweis auf schlecht kontrollierten Diabetes mellitus und geht mit einem erhöhten Risiko für fetale Entwicklungsstörungen und Anomalien einher. Eine aktuelle Untersuchung konnte nachweisen, dass Schwangere mit vorbestehendem Diabetes mellitus und nicht ausreichender glykämischer Kontrolle (>7,0 %) sowie einer erhöhten Nackentransparenz des Fetus ein deutlich erhöhtes Risiko für schwere fetale Fehlbildungen im ETS aufwiesen (Sensitivität 70,6 %; Spezifität 77,4 %; positiv prädiktiver Wert 16,2 %; negativ prädiktiver Wert 97,7 %; $p < 0,001$) (63). Die Planung von Schwangerschaften und Therapieoptimierung sollte bei Frauen mit Diabetes Typ 1 oder Typ 2 bereits personalisiert vor dem Eintreten der Schwangerschaft erfolgen. Die enge interdisziplinäre Zusammenarbeit der einzelnen beteiligten Berufsgruppen und die Therapieadhärenz sind Schlüsselfaktoren, um diese Risiken zu reduzieren. Optimal wäre eine Einstellung des HbA1c-Werts und demnach der glykämische Kontrolle bereits präkonzeptionell.

Einige Schwangere entwickeln im Laufe der Schwangerschaft einen GDM. Dieser gilt als Glukosestoffwechselstörung, die erstmals in der Schwangerschaft diagnostiziert wird. 2021 waren 8,5 % aller Schwangeren von einem GDM betroffen (67, 68). Es zeigten sich in den letzten Jahren eine steigende Prävalenz (4,6 % 2013) und ein Zusammenhang mit dem mütterlichen Alter (≥45 Jahre 12,5 % vs. <20 Jahre 3,6 %). Als Risikofaktoren für die Entwicklung eines GDM stehen unter anderem eine genetische Prädisposition sowie mütterliches Übergewicht und ein ungünstiger Lebensstil (Ernährung, Bewegung) im Vordergrund (61). Aktuelle Untersuchungen weisen darauf hin, dass Schwangere mit GDM verschiedene metabolische Profile aufweisen können, die mit unterschiedlichen geburtshilflichen Komplikationen assoziiert sind (69-71). Es konnten bestimmte Risikofaktoren identifiziert werden, die mit einer höheren Wahrscheinlichkeit für einen komplizierten Verlauf des GDM und Insulinabhängigkeit verbunden sind. Rostin *et al.* hat einen einfachen Score aus Daten wie den Blutzuckerwerten des 75-g-oGTT, dem Alter, dem BMI, der Gravidität und der Parität entwickelt, den wir prospektiv prüfen werden (CHANGED

Score, Manuskript aktuell im Peer-Review-Prozess). Zukünftig können Schwangere mit GDM risikoadaptiert und personalisiert betreut werden, um mögliche Komplikationen bereits vor der Entstehung zu adressieren und ein optimales Outcome für Mutter und Kind zu garantieren.

1.7. Risikokonstellation Uterusoperationen

Operative Eingriffe am Uterus können Auswirkungen auf die zukünftigen Schwangerschaften haben und erfordern eine besonders sorgfältige medizinische Betreuung. Vorangegangene Uterusoperationen, wie ein Kaiserschnitt oder die Myomenukleation, können zu einer komplexen Risikokonstellation in der Schwangerenbetreuung führen.

Insgesamt steigt die Sectio-Rate weltweit. In Deutschland lag die Rate der Kaiserschnittentbindungen 2021 bei 30,9 %. Im Vergleich dazu war die Rate 1991 mit 15,3 % deutlich niedriger (72). Ähnlich verhält es sich beim globalen Trend: Die durchschnittliche Kaiserschnittrate im Jahr 2021 betrug 21,1 % mit der höchsten Rate in den Industrieländern (27,2 %) und der niedrigsten in Entwicklungsländern (8,2 %) (73). Die steigende Sectio-Rate geht mit einem erhöhten mütterlichen Risikoprofil einher, da in der Folgeschwangerschaft das Risiko für Komplikationen erhöht sein kann (74). Zu den möglichen Komplikationen gehören Uterusruptur, Uterusdehiszenz, Narbenschwangerschaft und Plazentationsstörungen (75-77). Andere Risiken sind Verwachsungen und assoziierte operative Komplikationen sowie reduzierte Fertilität (78-80). Diese Konstellation hat einen Einfluss auf die Kurz- und Langzeitmortalität in Bezug auf mütterliche und kindliche Komplikationen und führt damit zu einer gesteigerten sozioökonomischen Belastung (81).

Die vaginale Geburt nach einem Kaiserschnitt (Trial of Labor After Cesarean = TOLAC, Vaginal Birth After Cesarean = VBAC) ist eine Option, um die Kaiserschnittrate insgesamt zu senken. Ein VBAC ist jedoch mit einem erhöhten Risiko für eine Uterusruptur assoziiert. Die Uterusruptur bezeichnet im Gegensatz zur uterinen Dehiszenz die komplette Trennung der gesamten uterinen Wand, also von Endometrium, Myometrium und Serosa (77). Bei der uterinen Dehiszenz sind die Serosa und das Amnion noch intakt. Beide Krankheitsbilder sind mit einer erhöhten peripartalen Mortalität und Morbidität assoziiert (75, 82). Für die Darstellung und die Beurteilung des unteren Uterinsegments ist der Ultraschall essentiell (Abbildung 6).

Das Rupturrisiko steigt im Zusammenhang mit einer Geburtseinleitung und der Verwendung von kontraktionsfördernden Medikamenten wie Oxytocin bzw. Prostaglandin sowie bei einem kurzen Intervall zwischen den Schwangerschaften (83, 84). Ein Abstand von unter zwölf Monaten zwischen den Schwangerschaften war mit einem zweifach erhöhten Risiko der Uterusruptur assoziiert (83). Die Wahl zwischen einem VBAC oder einem erneuten Kaiserschnitt ist eine komplexe Entscheidung, über die nach ausführlicher Untersuchung und in Rücksicht auf die Wünsche und Ängste der Schwangeren beraten werden kann. Die individuellen Umstände und Risiken jeder Frau spielen dabei eine entscheidende Rolle.

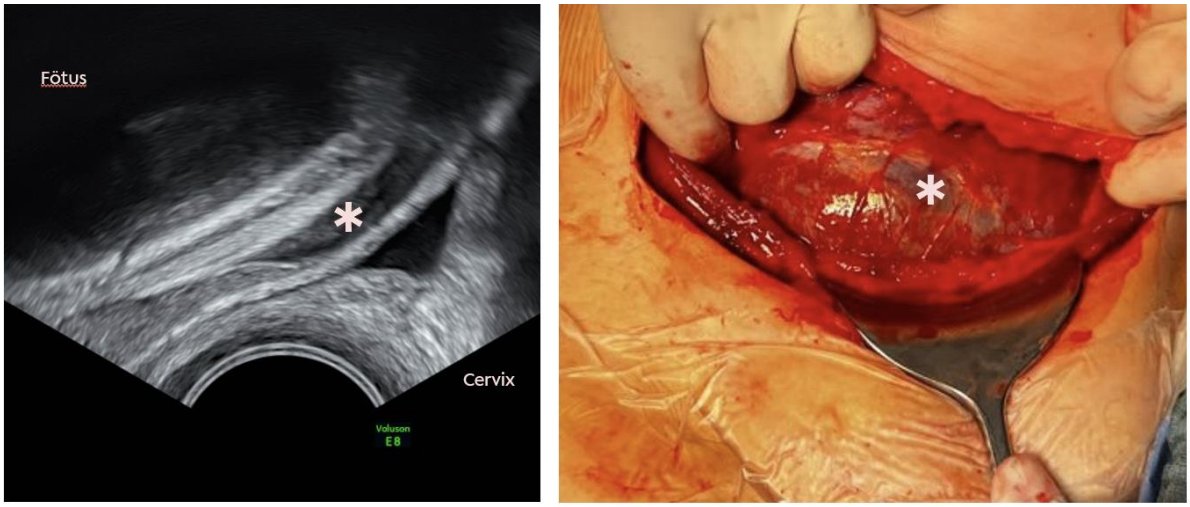

Abbildung 5: *Klinisches Bild einer uterinen Dehiszenz. Links sonographische Darstellung der Unterbrechung des Myometriums im unteren Uterinsegment (*), rechts das klinische Bild der uterinen Dehiszenz (*) im operativen Situs. Das Intervall zwischen den Schwangerschaften lag bei der Patientin bei unter zwölf Monaten. Aufnahmen von der Autorin. Mit freundlicher Genehmigung der Patientin.*

2. Ausgewählte Originalarbeiten

2.1. Antenatal body mass index (BMI) and weight gain in pregnancy – its association with pregnancy and birthing complications

Übergewicht und Adipositas sind ein schwerwiegendes Gesundheitsrisiko mit insgesamt zunehmender Inzidenz weltweit. Dies betrifft auch die Geburtsmedizin: Immer mehr Frauen sind in ihrer reproduktiven Phase übergewichtig oder adipös (BMI > 25,0) (34, 47) (Kapitel 1.5). Zusätzlich nehmen viele Schwangere in der Schwangerschaft übermäßig an Gewicht zu. In dieser Arbeit werden die Fragen untersucht, wie sich der allgemeine Trend der Gewichtszunahme gestaltet und was geschieht, wenn schwangere Frauen mehr Gewicht zunehmen als empfohlen. Studien konnten bereits belegen, dass gestationsbedingtes Übergewicht einen negativen Einfluss auf das kindliche und das maternale Outcome hat.

Für diese Analyse wurden geburtshilfliche Daten von 591 Schwangeren retrospektiv untersucht. Die Gewichtszunahme wurde anhand der Empfehlungen der IOM-Guidelines (Institute of Medicine, 2009) analysiert, basierend auf den präkonzeptionellen BMI der Schwangeren (Untergewicht, Normalgewicht, Übergewicht, Adipositas).

Insgesamt zeigte sich, dass 29 % der Kohorte mit einem BMI von mehr als 25,0 übergewichtig war. Die allgemeine Gewichtszunahme war in allen Gruppen ähnlich mit 12,0 bis 14,0 kg, trotz unterschiedlicher Empfehlungen in den BMI-Gruppen laut IOM-Guideline. Es nahmen 37 % der Frauen mehr Gewicht zu als von den IOM-Guidelines empfohlen (p-Wert < 0,001). Die Ergebnisse zeigten, dass Schwangere mit übermäßiger Gewichtszunahme ein erhöhtes Risiko für Geburtseinleitung aufwiesen (55,0 % vs. 45,7 %; p-Wert = 0,007). Zusätzlich ergab sich, dass Frauen mit übermäßiger Gewichtszunahme ein höheres Risiko für eine Geburt per Kaiserschnitt hatten (sekundäre Sectio, 22,4 % vs. 15,4 %; p-Wert = 0,008). Die Chance für eine Schwangere mit übermäßiger Gewichtszunahme, ihr Kind auf vaginalem Wege auf die Welt zu bringen, war niedriger als für Frauen mit Gewichtszunahme im Bereich der Empfehlung der IOM-Guidelines (57,5 % vs. 61,4 %; p-Wert = 0,008).

Zusammenfassend zeigt die Analyse, dass die Gewichtszunahme in der Schwangerschaft einen Einfluss auf das geburtsmedizinische Outcome hat. Die Beurteilung der Gewichtszunahme sollte nicht absolut anhand von Werten erfolgen (kg), sondern personalisiert basierend auf den präkonzeptionellen BMI. Zur Beurteilung der maternalen

Gewichtszunahme stehen die IOM-Guidelines zur Verfügung, die für jede BMI-Klasse explizite Empfehlungen herausgeben. In Zukunft sollte im Mutterpass der präkonzeptionelle BMI klar ersichtlich sein und so eine angemessene Beurteilung der Gewichtszunahme in der Schwangerschaft erfolgen. Möglicherweise könnten so auch Interventionen initiiert werden. Aktuell erfolgt eine retrospektive Datenanalyse von mehr als 2000 Schwangeren mit dem Fokus auf mütterliche Gewichtszunahme und geburtsmedizinische Komplikationen.

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Antenatal body mass index (BMI) and weight gain in pregnancy – its association with pregnancy and birthing complications

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Abstract

Background: Overweight and obesity is a serious health risk in both developed and developing nations. It is a common finding among women in their reproductive age. Half of patients entering their pregnancy in the US have a BMI >25.0 and therefore qualify as overweight or obese. Moreover, there is a tendency towards increased weight gain during pregnancy. Studies have shown that gestational overweight is associated with complications in pregnancy and birthing as well as short-term and long-term impacts on neonatal outcome in childhood and adulthood.
Methods: Five hundred and ninety-one women visiting our tertiary perinatal center in 2014 were analyzed for antenatal BMI, gestational weight gain, as well as pregnancy outcome and complication together with neonatal weight and outcome. Pregnancy weight gain was assessed based on the IOM guidelines (Institute of Medicine) issued in 2009.
Results: Twenty-nine percent of our population was overweight with a BMI of more than 25.0. The general weight gain was in every BMI group similar (median ranging from 12.0 to 14.0 kg). Approximately one third gained more than the appropriate amount (37%, P<0.001). Women with more gestational weight were at risk of labor induction (55.0% vs. 45.7% labor induction in total, P=0.007). Strikingly, those patients were found to have significantly higher rates of secondary cesarean section (22.4% vs. 15.4%) and decreased chances of spontaneous vaginal birth (57.5% vs. 61.4%) (P=0.008). Furthermore women with a pregnancy weight gain in excess of the guidelines gave birth to neonates with a higher birth weight (>75.centile, 28.3% vs. 21.3%, P<0.001).
Conclusions: Altogether, one third of the analyzed population is already overweight or obese when entering pregnancy. A higher gestational weight gain than the recommended amount was found in 37% of cases. We found an association with pregnancy and birthing complications as well as higher infant weight. This highlights the importance of preconceptive and prenatal advice, and if necessary, intervention on BMI and weight gain.

Keywords: Antenatal BMI; body mass index; gestational weight gain (GWG); IOM recommendations/guidelines; large for gestational age (LGA); macrosomia; obesity; obesity-related complications; pregnancy; small for gestational age (SGA).

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Introduction

Overweight and obesity is a world-wide acknowledged serious health risk, associated with cardiovascular complications, diabetes and its consequences, as well as other diseases. In Germany, along with the world-wide developemt, the rates of overweight and obesity have increased in recent decades. Data from the Organisation for Economic Cooperation and Developement (OECD) revealed an obesity rate among adults in Germany of 14.7% in 2009 compared to 11.5% in 1999 (data is based on self-reported BMI) [1]. The incidence of overweight among German adults was 52.4% in 2013 compared to 45.8% in Italy and 63.2% in the US [1]. These findings display that Germany is a contries with one of the highest rates of overweight within the European Union.

Overweight and obesity among women in their childbearing age is considered to be a particular issue. Studies have shown that around 50% of women have a preconceptive BMI of more than 25.0 in the United States and Australia and are therefore overweight [2, 3]. In the UK, 20% of all women in their childbearing age are obese with a BMI of more than 30.0 [4]. There is evidence that overweight and obesity in pregnancy is associated with serious pregnancy complications such as hypertension, preeclampsia and gestational diabetes [5, 6]. In addition,

research has highlighted a correlation to other birthing risks, such as the need for induction of labor, perineal tear or cesarean section, as well as higher infant birth weight [2, 3]. There are also indications suggesting a poor neonatal outcome and a link to childhood and adulthood overweight and obesity [7–9].

In short, there is a growing hazard resulting from the increasing incidence of overweight and obesity in the reproductive age of women and its overall consequences on the health system. These alarming findings emphasize the importance of research in this field as well as an establishment of documentation and interventions in order to limit gestational weight gain.

Due to this trend toward more overweight and obesity in pregnancy in the past two decades, the Institute of Medicine, a North American non-profit non-governmental organization, issued revised gestational weight gain guidelines in 2009. On the basis of these guidelines, the German Diabetes Association (DDG) and the German Association of Gynecology and Obstetrics (DGGG) released updated recommendations for weight gain in pregnancy in 2011. In our research we applied these guidelines.

Methods

Study design and population

This is a retrospective, descriptive observational study. BMI, weight gain and pregnancy as well as birthing complications and neonatal outcome of 591 women that previously presented at our tertiary perinatal center were registered and filed anonymously. The presenting patients were of Caucasian origin. Birthing protocols (containing gestational week, mode of delivery, birthing outcome, neonatal and maternal outcome) were analyzed retrospectively. Prepregnancy weight and height was obtained from the information given in the "Mutterpass". In most cases this means self-reported measures before the pregnancy. Antenatal BMI was grouped into four categories: underweight (BMI<18.5), normal weight (BMI 18.5–24.9) and overweight (25.0–29.9), as well as obesity (≥30.0). Gestational weight gain at time of birth was evaluated using the IOM guidelines according to the gestational week. It is worth noting that the IOM recommendations only go as far as 40 gestational weeks. In the event of of 41 or 42 gestational weeks, we added the amount of weight per week that is suggested for the second and third trimester given in Table 1, according to the BMI group.

Mode of delivery (spontaneous vaginal birth, forceps/ventouse, secondary and primary cesarean section) was assessed as well as birthing complications (episiotomy and perineal tear ≥2nd degree) in cases of vaginal birth. Rates of gestational diabetes, hypertension and preeclampsia were noted. Neonatal birth weight together with outcome (pH and Apgar) was registered. Statistical analysis was performed using SPSS, Version 20. Applied tests were *t*-test, ANOVA, Mann-Whitney *U*-test, an Fisher's exact test.

Table 1: Recommendations for total and rate of weight gain during pregnancy, by prepregnancy BMI.

Prepregnancy BMI	BMI (kg/m²)	Total weight gain (kg)	Rates of weight gain 2nd and 3rd trimester (kg/week)
Underweight	<18.5	12–18	0.45–0.58
Normal weight	18.5–24.9	11.5–16	0.36–0.45
Overweight	25.0–29.9	7–11.5	0.22–0.32
Obese	≥30.0	5–9	0.18–0.27

The calculations presume a weight gain of 0.5–2 kg in the first trimester. Taken and revised from [10].

Results

Among 591 patients 175 displayed an antenatal BMI of ≥25.0 (29% in total). Sixty percent of these women had a BMI ranging from 25.0 to 29.9 (106 out of 175; or 18% of all women, 106 out of 591) and were consequently overweight. Forty percent of these 175 patients were obese with a BMI of more than 30.0 (69 out of 175; 12% of all women, 69 out of 591). Sixty-five percent (367 out of 591) of patients were within the normal weight range (BMI 18.5–24.9). Only 8% were found to be underweight with a BMI of <18.5 (49 out of 591).

Interestingly, weight gain was found to be very similar in all BMI groups. The median is ranging from 12.0 to 14.0 kg as opposed to the IOM weight gain recommendations (Tables 1 and 2) that give specific spans of pregnancy weight increase for each BMI group.

Notably, over a third of the patients gained more weight than the recommended amount (37%, 219 out of 591) (Table 3). Only 44% of women displayed an increase in gestational weight within the suggested range (260 out of 591). Nineteen percent of patients gained less weight than recommended (112 out of 591).

Table 2: Weight gain in each BMI group.

	BMI group			
	<18.5	18.5–24.9	25–29.9	≥30
Weight gain (kg)				
Average	13.3	14.2	14.8	12.5
Standard deviation	4.4	5.6	6.4	7.1
Median	13.0	14.0	14.0	12.0
Minimum	2	2	0	−5
Maximum	22	50	35	28
Number of patients	49	367	106	69

Overall gestational weight gain was found to be similar in all BMI groups, unlike the IOM guidelines that suggest a specific range for each BMI group.

Table 3: Gestational weight gain in relation to IOM recommendations.

	Weight gain correlated to IOM guidelines		
	Within	Above	Under
Weight gain (kg)			
Average	12.5	19.3	7.3
Standard deviation	2.8	5.1	2.8
Median	12.5	19.0	8.0
Minimum	5	10	−5
Maximum	29	50	12
Number of patients	260	219	112

Thirty-seven percent of all women gained more weight than recommended for their BMI.

Women that gained pregnancy weight above the IOM recommendations had a significantly higher risk of labor induction (55.0% vs. 45.7% in total, P=0.007) (Table 4).

Interestingly, patients with a pregnancy weight increase above the suggested range exhibited a significantly higher risk of secondary cesarean section (22.4% vs. 15.4%) and lower incidence of spontaneous vaginal birth (57.5% vs. 61.4%) (P=0.008) compared to women with weight gain within or below the normal range (Table 5 and Figure 1).

Results concerning birthing traumas (such as perineal tear, ≥grade II or episiotomy) were inconclusive. 65.7% of spontaneous vaginal or ventouse deliveries had no birthing trauma (n=315) compared to 19.4% who received an episiotomy (n=76) and 14.8% of patients had a perineal tear of ≥grade II. No significant correlation with the amount of gestational weight gain was observed.

Table 4: Gestational weight gain and the risk of labor induction.

	Labor induction		Total
	No	Yes	
Weight gain compared to IOM guidelines			
Within			
n	127	85	212
%	59.9	40.1	100.0
Above			
n	81	99	180
%	45.0	55.0	100.0
Under range			
n	53	36	89
%	59.6	40.4	100.0
Total			
n	261	220	481
%	54.3	45.7	100.0

Significantly higher risk observed in women with pregnancy weight increase above the IOM guidelines.

Table 5: Weight gain according to the IOM recommendations compared to mode of delivery.

Weight gain compared to IOM guidelines	Mode of delivery				Total
	Spontaneous vaginal birth	Forceps/ ventouse	Primary cesarean	Secondary cesarean	
Within					
n	163	18	48	31	260
%	62.7	6.9	18.5	11.9	100.0
Above					
n	126	5	39	49	219
%	57.5	2.3	17.8	22.4	100.0
Under range					
n	74	5	22	11	112
%	66.1	4.5	19.6	9.8	100.0
Total					
n	363	28	109	91	591
%	61.4	4.7	18.4	15.4	100.0

Women who gained more than the recommended weight were at higher risk of secondary cesarean section and had lower incidence of spontaneous vaginal birth (P=0.008).

Concerning neonatal birth weight, we were able to demonstrate in our study that patients who gained pregnancy weight above the IOM guidelines had a significant risk of giving birth to infants with higher birth weight (birth weight above the 75th percentile, 28.3% vs. 21.3%). Conversely, women that gained less weight than the recommended amount, were found to have children with significantly lower birth weight compared to patients with gestational weight gain within or above the IOM guidelines (6.3% vs. 21.3%) (Table 6). In our research we used the 75th percentile as a cut-off to distinguish between higher and lower birth weight. The incidence of LGA and SGA neonates in our cohort were too low in order to produce a statistically significant statement. In a descriptive analysis we found a tendency towards more LGA children (birth weight above the 97th percentile) in the group of gestational weight gain above the IOM guidelines (5.5% vs. 3.7%, P=0.023). No LGA neonates were born to those women with gestational weight gain below the IOM recommendations (Table 7).

Concerning the incidence of gestational diabetes among our population, we were able to demonstrate a significantly higher risk of developing gestational diabetes among patients with a BMI of ≥25.0 compared to those

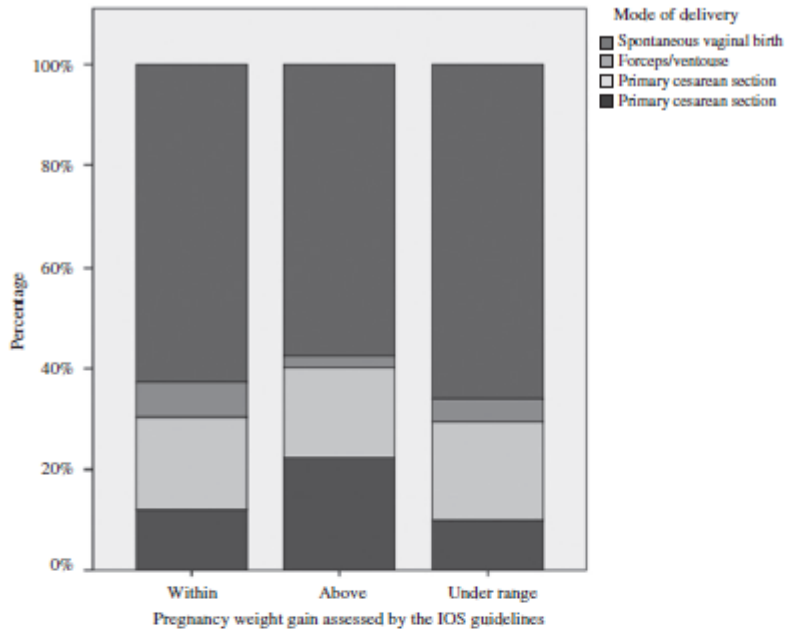

Figure 1: Weight gain compared with mode of delivery. Women who gained more weight than the IOM-recommended amount were at higher risk of secondary cesarean section and showed less rates of spontaneous vaginal birth (P=0.008).

with a BMI of ≤24.9 (23.4% vs. 11.3%, P=0.035). No correlation between the amount of gestational weight gain (especially above the IOM guidelines) and the incidence of gestational diabetes could be found (Table 8).

Table 6: Weight gain according to the IOM recommendations compared to infant birth weight, P>0.001.

	Percentile groups		Total
	≤75th percentile	>75th percentile	
Weight gain compared to IOM guidelines			
Within			
n	203	57	260
%	78.1	21.9	100.0
Above			
n	157	62	219
%	71.7	28.3	100.0
Under range			
n	105	7	112
%	93.8	6.3	100.0
Total			
n	465	126	591
%	78.7	21.3	100.0

In this study we used the 75th percentile as a cut-off to distinguish between higher and lower birth weight. Women with a gestational weight gain above the IOM guidelines were found to be at higher risk of giving birth to larger infants.

Discussion

Principal findings

In a representative group of patients (n=591) we analyzed the development of gestational weight within four BMI

Table 7: Incidence of LGA neonates (≥97th percentile) among women with gestational weight gain within, above and below the IOM recommendations (P=0.023).

	Percentile groups		Total
	<97th percentile	≥97th percentile	
Weight gain compared to IOM guidelines			
Within			
n	250	10	260
%	96.2	3.8	100.0
Above			
n	207	12	219
%	94.5	5.5	100.0
Under range			
n	112	0	112
%	100.0	0.0	100.0
Total			
n	569	22	591
%	96.3	3.7	100.0

Table 8: Prevalence of gestational diabetes among patients with a BMI of 25.0 and higher is significantly increased compared to those with a BMI of 24.9 and lower (P=0.035).

BMI groups		Gestational diabetes		Total
		No	Yes	
≤24.9	Weight gain compared to IOM guidelines			
	Within			
	n	185	20	205
	%	90.2	9.8	100.0
	Above			
	n	101	12	113
	%	89.4	10.6	100.0
	Under range			
	n	83	15	98
	%	84.7	15.3	100.0
	Total			
	n	369	47	416
	%	88.7	11.3	100.0
≥25.0	Weight gain			
	Within			
	n	38	17	55
	%	69.1	30.9	100.0
	Above			
	n	83	23	106
	%	78.3	21.7	100.0
	Under range			
	n	13	1	14
	%	92.9	7.1	100.0
	Total			
	n	134	41	175
	%	76.6	23.4	100.0
	Total sum			
	n	503	88	591
	%	85.1	14.9	100.0

groups compared to the IOM guidelines. About one third of women had a prepregnancy BMI more than 25.0 and were therefore considered either overweight or obese. This is a distressing statistic, highlighting the high incidence of overweight and obesity among women of childbearing age in Germany. In the US and Australia the situation is more severe, with 50% of women found to have a preconceptive BMI of more than 25.0 [2, 3]. In the UK 20% of all women in their reproductive age have a BMI of 30.0 and more [11]. Those alarming findings make overweight and obesity and their associated complications a common risk among pregnant women in 2015.

Weight gain during pregnancy result from maternal fat deposit, plasma expansion, peripheral edema, placental and fetal mass as well as amniotic fluid. According to the gestational week, different amounts of weight gain are recommended (IOM guidelines from 2009, table 1). It appears difficult to determine which of the contributors to maternal weight are responsible for associated pregnancy and birthing complications. Research has shown that the accumulation of fat tissue is responsible for obesity-related complication, mostly through insulin resistance and diabetes [2, 11, 12]. Furthermore, fat deposits narrow the pelvic outlet and are very likely to cause complications in labor and birthing [13].

Surprisingly, patients in this study across all four BMI groups increased pregnancy weight similarly (12.0 to 14.0 kg, table 2) in contrast to the IOM guidelines that suggest specific weight gain for each BMI group (table 1). In total, more than one third of women (37%) gained gestational weight above the IOM recommendations (table 3). Only 44% of patients had a gestational weight gain within the recommended range, while 18% fell below. These findings highlight the high incidence excessive weight gain in our study population and suggest the need for early advice (primary/secondary prevention) and, when required, intervention in the preconceptive and prenatal consulting.

Pregnancy and birthing risks associated with high gestational weight gain: labor induction and cesarean section

Cases of labor induction were significantly higher in women with gestational weight gain above the IOM recommendations (55.0% vs. 45.7% in total, P=0.007, Table 4). Wispelwey et al. highlight in their review that obese women have a higher incidence of labor induction and cesarean delivery [14]. In one study, the odds to receive induction of labor for obese women compared to normal weight patients were at 2.53 to 1 [15]. Furthermore another group revealed a positive correlation between additional weight and a decrease in cervical dilation rate [13].

In accordance with other studies [11, 13, 14, 16], we have shown that women with higher gestational weight gain were more likely to receive secondary cesarean section (22.4% vs. 15.4%, P=0.008, Table 5 and Figure 1). Dietz et al. analyzed a cohort of 24,423 nulliparous women in the US, revealing that women with higher antenatal BMI are more prone to give birth by cesarean section compared to normal weight patients (42.6% BMI ≥35.0 vs. 14.3% BMI <19.8) [16].

Results concerning birthing injuries were inconclusive in this study. No significant correlation with the amount of gestational weight gain was observed. There is evidence in literature that higher infant birth weight is associated with an increased incidence of perineal trauma

or episiotomy [17, 18]. A recent prospective observational study from the UK (n=3000) showed a higher risk of perineal trauma in women who gave birth to children with higher birth weight [17]. A systematic review by Dudding et al. revealed risk factors for severe perineal trauma (≥3rd degree perineal tear) such as high infant birth weight (more than 4000 g), prolongation of second stage of labor, instrumental vaginal delivery and episiotomy as well as occipital posterior position [18]. An Australian trial by Hauck et al. found evidence that higher infant birth weight provides a risk for severe perineal trauma. However, no association between BMI and severe perineal trauma could be confirmed [19].

Higher gestational weight gain is correlated to higher infant birth-weight

We have shown that higher gestational weight gain leads to an increased infant birth weight for neonates with a birthweight above the 75th percentile (28.3% vs. 21.3%, P>0.001, Table 6). Additionally, our results reveal a trend towards a higher incidence of macrosomic children (above the 97th percentile) among women with gestational weight gain above the IOM recommendations (5.5% vs. 3.7%, P=0.023, Table 7). Overweight through higher gestational weight gain has an impact on intrauterine nutrition and growth. Literature revealed a positive correlation due to over-nutrition causing infant's obesity [20, 21]. High infant birth weight has an influence on the neonate's metabolic system and is therefore associated with a higher chance of overweight and obesity and other metabolic disorders in childhood and adulthood [7–9, 22]. A recent meta-analysis by Aune et al. confirmed that infants born to mothers with an increased BMI are at risk of fetal death, stillbirth and infant death [23].

Gestational diabetes

This study demonstrated a significantly higher risk of developing gestational diabetes among patients with a BMI of ≥25.0 compared to those with a BMI of ≤24.9 (23.4% vs. 11.3%, P=0.035) (Table 8). Ding et al. were able to demonstrate a very similar finding among a cohort of 13,121 patients: women with an increased pre-pregnancy BMI were at higher risk of developing gestational diabetes (ARR 3.4, 95% CI 2.3–5.2) [24]. No association between increased gestational weight gain and the incidence was found in our research. This is in contrast to the results of a recent meta-analysis by Brunner et al. which demonstrated a relation between excessive gestational weight gain and the incidence of gestational diabetes among a total of 13,748 patients [25]. This might be explained by the somewhat limited data in our study. Mothers who developed gestational diabetes are at a seven-fold higher risk of developing type 2 diabetes [26]. A higher incidence of preeclampsia and cesarean delivery was found in patients diagnosed with gestational diabetes [27, 28].

Studies have shown that hyperglycemia results in excessive weight gain of the fetus. The HAPO trial revealed a linear correlation of glucose levels and birth weight [29]. Neonates born to mothers with gestational diabetes are at a relative risk of being macrosomic (>4000 g) of 1.81 (95% CI 1.47–2.22, P<0.001) as shown in a meta-analysis by Wendland et al. [28].

Strength and limitations of this study

This study is novel as it analyzes pregnancy, birthing and neonatal complications on the basis of the IOM guidelines in a large representative group of patients. It not only assesses the risks of patients that are already overweight or obese, but also those who are normal weighing. Generally, the results confirm findings that were observed in daily clinical life and which are correspond well with results of other groups. We demonstrated the significantly higher risk of labor induction, secondary cesarean section and higher infant birth weight in women gaining more than the appropriate amount of gestational weight.

What about the self-reporting nature of the data collection from the patients? It is imaginable that there might be a trend towards underreporting weight.

As for limitations, the results cannot prove the cause of correlations we were able to show. Potential connections are discussed, but further interdisciplinary research has to be conducted in order to confirm causation.

In the future, a higher number of patients would be preferable to analyze more pregnancy complications such as preeclampsia, premature rupture of membranes, premature delivery, intrauterine growth retardation and many others. Additionally, ethnic differences in gestational weight gain and the resulting outcomes would be interesting to analyse as our tertiary perinatal center has a large south Asian patient cohort.

Conclusion

In summary, this study confirms that high gestational weight gain has an impact on pregnancy and birthing complications as well as infant birth-weight.

Generally, higher gestational weight potentially compromises the patient's and neonate's health and subsequently affects the healthcare system in the long term. An interdisciplinary approach to document antenatal BMI and make preventative interventions is required [30, 31]. General practitioners, obstetricians and gynecologists as well as nurses and midwifes need to cooperate in this approach. Other disciplines, such as dieticians, psychologists, endocrinologists and personal trainers should be consulted in cases of need for intervention. Intervention techniques should be standardized, and education of the families and the public established for the patient's support. Gestational weight gain must be documented in relation to the antenatal BMI group according to the IOM guidelines. Patients with high gestational weight gain should get critical attention and advice in their prenatal care early on. Delivery ought to be referred to a tertiary perinatal center, where obstetricians and midwives are aware of potential complications and can therefore act in a timely manner.

This study contributes to a very current issue. Further studies, preferably German- or Europe-wide, have to be conducted. Panels of experts should be convened in order to form general recommendations on intervention in gestational weight gain.

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2.2. Cervical ripening after cesarean section: a prospective dual center study comparing a mechanical osmotic dilator vs. prostaglandin E2

Bei ungefähr 20% der Schwangerschaften ist eine Geburtseinleitung nötig (85). Für die Einleitung kann es geburtshilfliche, mütterliche und kindliche Gründe geben (86). Viele dieser Indikationen lassen sich im Rahmen der Schwangerenvorsorge feststellen. Im 21. Jahrhundert wurde eine Vielzahl von medikamentösen und mechanischen Methoden zur Geburtseinleitung entwickelt, die risikoadaptiert angewendet werden können: Prostaglandin E2 (Dinoproston), Prostaglandin E1 (Misoprostol), der Ballonkatheter, der hygroskopische Dilatator und Oxytocin sind die am häufigsten verwendeten Medikamente bzw. Produkte zur Zervixreifung und Geburtseinleitung (Abbildung 8) (85-87). Mechanische Methoden zur Zervixreifung zeigen die geringste Rate an Nebenwirkungen wie uterine Überstimulation und pathologisches CTG (88-91).

Auch bei Frauen mit einer Uterusnarbe nach einem Kaiserschnitt ist die Zervixreifung eine Option. Die Anwendung des osmotischen Dilatators ist im Gegensatz zu Prostaglandinen in dieser besonderen Patientinnengruppe kein Off-Label-Use. Es wird vermutet, dass mechanische Methoden zur Zervixreifung bedingt durch die spezifische Wirkweise insgesamt eine reduzierte Rate an Uterusruptur aufweisen (92). In dieser prospektiven Analyse wurden Frauen eingeschlossen, bei denen eine Indikation zur Geburtseinleitung vorlag und die einen TOLAC angestrebt haben. Die Analyse wurde an zwei Zentren in Berlin durchgeführt. Es wurde mit Dilapan-S eine mechanische Methode zur Zervixreifung untersucht, die bei Frauen mit einer Sectio in der Anamnese nicht kontraindiziert ist. Dilapan-S ist ein osmotischer hydrophiler Dilatator, der in den Zervikalkanal eingelegt wird und dort graduell an Umfang zunimmt. Es wird eine langsame Reifung der Zervix angenommen. In die Studie wurden insgesamt prospektiv 104 schwangere Frauen aufgenommen, die eine Zervixreifung mit Dilapan-S erhielten. Als Kontrollgruppe diente eine historische Kohorte von 102 Frauen, bei denen im Off-Label-Use Prostaglandine angewandt wurden (vor 2013). Es ergaben sich keine Unterschiede in Bezug auf das unmittelbare neonatale Outcome in beiden Gruppen. Die Rate an vaginalen Geburten war insgesamt in beiden Gruppen ähnlich mit 52 % bei Dilapan-S-Einsatz im Vergleich zu 53 % in der historischen Kohorte. Die Ergebnisse zeigen einen signifikanten Unterschied im Hinblick auf das Intervall von Applikationen bzw. Anwendung bis zum Geburtsbeginn: Frauen aus der Dilapan-S-Gruppe wiesen ein deutlich längeres Intervall

auf als Frauen der historischen Kohorte (37,9 im Vergleich zu 20,7 Stunden, *p*-Wert < 0,001). Das kann durch die unterschiedliche Wirkweise beider Methoden erklärt werden. Das Zeitintervall zwischen Geburtsbeginn und Geburt war in beiden Gruppen gleich (Dilapan-S 7,93 im Vergleich zu Prostaglandin 7,44 Stunden, *p*-Wert = 0,758). Insgesamt konnte die Untersuchung zeigen, dass die mechanische Methode eine gute Option für die Zervixreifung bei TOLAC ist. Im Fall von Dilapan-S handelt es sich nicht um Off-Label-Use, was in der heutigen Situation mit drohenden juristischen Sanktionen ebenfalls einen bedeutenden Beweggrund darstellt.

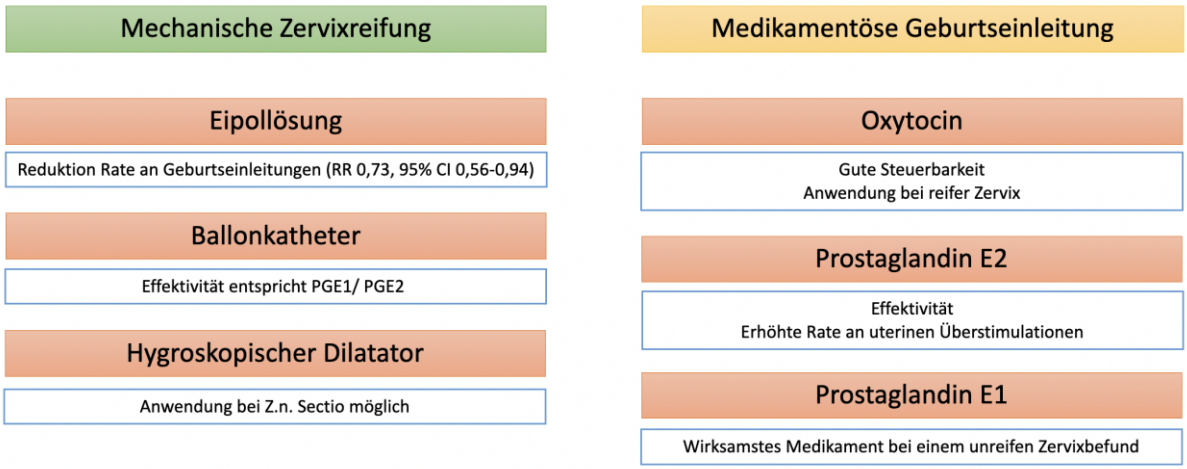

Abbildung 6: *Übersicht der Möglichkeiten zur Zervixreifung bzw. Geburtseinleitung. Die Unterteilung erfolgte hier nach mechanischer und medikamentöser Wirkweise. Grafik von der Autorin. Aktuelle Evidenz der jeweiligen Methode nach (85).*

Aktuelle Studien zeigen, dass die mechanische Zervixreifung auch im ambulanten Setting in einem Niedrigrisikokollektiv eine Option ist (91). Durch die ambulante Zervixreifung kann eine Reduktion der sozioökonomischen Kosten erreicht werden. Dies wird durch einen insgesamt kürzeren Krankenhausaufenthalt, eine verringerte Zeitspanne von der Aufnahme bis zur Geburt und weniger Anwendung von Kontraktionsmitteln vermutet (91).

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Cervical ripening after cesarean section: a prospective dual center study comparing a mechanical osmotic dilator vs. prostaglandin E2

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Abstract

Objectives: Worldwide, the overall cesarean section is rising. Trial of labor after cesarean (TOLAC) is an overall safe option with an immediate impact on neonatal and maternal short- and long-term health. Since the use of prostaglandins in cervical ripening is associated with an increased risk of uterine rupture, mechanical methods as balloon catheters or osmotic dilators have been suggested for cervical ripening prior to induction of labour. Here we are analyzing and comparing the VBAC rate, as well as maternal and fetal outcome in cervical ripening prior to TOLAC.

Methods: This prospective dual center study analyses maternal and neonatal outcomes of TOLAC in women with an unfavorable cervix requiring cervical ripening agent. The prospective application of an osmotic dilator (Dilapan-S, n=104) was analysed in comparison to the retrospective application of off-label dinoprostone (n=102).

Results: The overall fetal and neonatal outcome revealed no significant differences in both groups. Patients receiving cervical ripening with the osmotic dilator delivered vaginally/by ventouse in 52% of cases, compared to 53% when using dinoprostone (p=0.603). The interval between application to onset of labor was significantly higher in the osmotic dilator group (37.9 vs.20.7 h, p=<0.001). However, time from onset of labor to delivery was similar in both groups (7.93 vs. 7.44 h, p=0.758). There was one case of uterine rupture in the dinoprostone group.

Conclusions: Our data shows that the application of the osmotic dilator leads to similar outcomes in VBAC rate and time from onset of labor to delivery as well as safety in both groups compared to off-label use dinoprostone. Cervical ripening using the mechanical dilator is a viable and effective option, without the risk of uterine hyperstimulation.

Keywords: cervical ripening; cesarean section (CS); cesarean section rate; osmotic dilator; repeat cesarean section (RCS); trial of labor after cesarean (TOLAC); unfavorable cervix; uterine scar; vaginal birth after cesarean (VBAC).

Key message

With the cesarean section rate rising, trial of labor appears as a viable option to counteract this trend. Overall, this analysis shows promising results on the efficiency and safety of the osmotic dilator in cervical ripening.

Introduction

Today, every third child in Germany is born via cesarean delivery. In 2018 the cesarean section (CS) rate in Germany was 29.1%, compared to 15.3% in 1991 [1]. In the OECD countries (Organisation for Economic Co-operation and Development) 28.1% of deliveries were via cesarean section [2]. An increasing number of women have a uterine scar after CS and they require counseling regarding their subsequent delivery. These patients are at a slightly increased risk of complications during labor and delivery, such as uterine rupture [3, 4].

There are two options for women who have undergone one prior CS: either elective repeat cesarean (RCS) or trial of labor after cesarean (TOLAC), with both methods of delivery associated with certain risks [5–7]. It is of utmost importance to counsel a patient and weigh the pros and

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cons of both options when planning the delivery after caesarean. RCS is associated with increased maternal and fetal morbidity, such as blood loss, injury of internal organs, scarring/adhesions, and placental abnormalities (placenta accreta, increta, percreta, previa) as well as respiratory problems necessitating breathing assistance and oxygen supplementation [5, 8]. TOLAC is associated with lower maternal/fetal morbidity and lower rates of complications in the following pregnancy [9, 10].

Statistically, 60–80% will have a successful VBAC, depending on the individual situation [10–17]. Due to the rising number of cesarean deliveries, the promotion of VBAC is a good tool to decrease the CS rate on the population level. Women that are eligible for TOLAC with an unfavorable cervix and the necessity to induce labor pose a dilemma for the obstetrician: oxytocin as an induction agent is not promising in a Bishop Score <6 and the application of prostaglandins is not recommended on expert opinion level. According to the manufacturer prostaglandin (such as the prostaglandin E2/dinoprostone) or the double balloon catheter are contraindicated in this subgroup of patients. The potential risk of uterine rupture is as high as 2.24% in prostaglandin-induced labor vs. 0.52% in spontaneous labor in TOLAC [18]. The likelihood of uterine rupture when applying prostaglandin is especially elevated in those women with an unfavorable cervix [19, 20]. Additionally, augmentation of labor in woman attributed to an increased risk of uterine rupture: 1.1% for oxytocin application, 0.9% for augmented labor and 0.4% for spontaneous labor [21]. Women with no prior vaginal delivery displayed a particularly increased likelihood of uterine rupture during TOLAC (1.5 vs. 0.8%, p=0.02) [21]. The application of mechanical agents, such as balloon catheters or osmotic dilators, is a viable option: the Foley catheter and the balloon catheter appears to be a safe tool with a vaginal birth rate of 56.4% [22]. Other mechanical devices are osmotic dilators or laminaria tents, made from sterile sea-weed or synthetic hydrophilic materials [23]. Another osmotic dilator, called Dilapan-S®, is not contraindicated for the application in patients with a previous CS [24]. Here we are comparing a prospective observational group of patients with the retrospective application of prostaglandin E2 (dinoprostone) in safety and efficacy.

Materials and methods

This is a prospective comparative dual-center pilot study including 104 pregnant women attempting TOLAC that received cervical ripening with the osmotic dilator between 2016 and 2020 at the "Vivantes Klinikum im Friedrichshain", a public tertiary care academic affiliate of Charité University, Berlin, Germany and a secondary perinatal center "Sana Klinikum Lichtenberg". This group was compared to a retrospective cohort of 102 patients that received dinoprostone between 2012 and 2007.

Included into this study were patients ≥18 years, with a gestational age ≥37/0, singleton pregnancies with cephalic presentation, one prior caesarean section with a low transverse uterine incision (operational technique was known), an unripe cervix (Bishop Score <6) and a medical indication for labor induction. No other conditions requiring primary RCS such as placenta praevia, vasa praevia, or severe diseases or indication for imminent delivery were apparent. Exclusion criteria were premature rupture of membranes, twins, or multiples.

We utilized a standardized protocol that implements cervical ripening by dinoprostone or the osmotic dilator as well as subsequent management of latent phase and active phase of labor (Figure 1). The osmotic dilator (Dilapan-S®) is a small rod made out of hydrophilic material. It is inserted into the cervical canal during a gynecological exam. Prior to insertion, a disinfectant appropriate for mucosal skin is applied (e.g. Octenisept®). Up to five rods can be inserted during one session and left for 12 h in the cervical canal. Removing the osmotic dilator and inserting a new one was repeated individually up to three times. The mechanical device acts by absorbing fluids in the cervix, increasing the rod circumference and consequently ripening, shortening and effacing the cervix. After the insertion fetal heart rate is monitored via CTG for 30 min. Patients of this subgroup are admitted to our labor ward and monitored regularly. If Bishop Score was ≥6, labor induction with oxytocin was continued. Oxytocin was administered intravenously (6IE in 500 mL) by an infusion pump, starting at 15 mL/h (0.18IE/h). Oxytocin flow is increased every 30 min, with the highest flow at 60 mL/h in this subgroup of patients (0.72IE/h). Once oxytocin administration is initiated, amniotomy had to be performed within 2 h.

Prostaglandin E2 (dinoprostone, Minprostin®) was applied as a vaginal gel insert during an internal vaginal examination (1 and 2 mg, max. 3 mg in 24 h), initially commenced with 1 mg and continued after 8 h. The agent was used for a maximum of 48 h (a total amount of 6 mg dinoprostone). Afterwards induction was continued with oxytocin, if the patient did not develop contractions.

Cervical status was assessed using the Bishop Score every time the osmotic dilator (every 12 h) or dinoprostone (every 8–12 h) was exchanged/applied or if the patient developed contractions. The Bishop Score is a score on a scale from 0 to 10 including cervical length, effacement, consistency, as well as position and station of the fetal head [25]. The score was originally introduced by Bishop in 1964 and further modified in 1966 by Burnett [26].

Fetomaternal surveillance was conducted via fetal heart rate tracing (CTG) and maternal vital signs (heart rate, blood pressure, oxygen saturation). During cervical ripening with the osmotic dilator, fetomaternal surveillance was performed for 30 min. Before the application of dinoprostone fetal well-being was confirmed for 15 min, followed by 90 min after the application, and for another 60 min 4 h after the application.

The primary outcome was mode of delivery, while the secondary was the interval from admission to delivery. Prior to induction of labor, the Bishop Score is assessed.

Uterine rupture is a full thickness tear of the uterine wall including the uterine serosa, whereas uterine dehiscence is defined as gradual myometrial rupture with intact membranes/serosa [27].

The power analysis calculated group sample sizes of 92 and 92, achieving 80% power to detect non-inferiority using a one-sided, two-sample t-test. Data was analysed using *R* version 3.2.5. Among others Fisher's Exact Test for count data, Kruskal-Wallis rank sum test, Pearson's Chi-squared test were utilized.

Ethical approval

Prior to the analysis, we requested an ethics committee meeting and received approval from the Ethics Committee of the Ärztekammer, Berlin (September 20th, 2016; Eth-37/16).

Results

Basic results

Data was collected from 104 women receiving cervical ripening with the osmotic dilator presenting at our tertiary perinatal clinic (Vivantes Klinikum im Friedrichshain) and a secondary perinatal center (Sana Klinikum Lichtenberg) vs. 102 receiving off-label dinoprostone. There were no significant differences in the baseline characteristics (Table 1). All patients had one previous CS and were approximately 31.8–32.6 years old and received cervical ripening at 41 weeks. The BMI was lightly overweight with 26.1–26.6. 76.9 vs. 77.4% (osmotic dilator, dinoprostone respectively) of women delivered one child prior via CS. Indication for induction of labor was for the most part for maternal reason (osmotic dilator 63% and dinoprostone 44%; for example gestational diabetes, diabetes, hypertension, preeclampsia/HELLP syndrome). Other indications were post-term pregnancy (osmotic dilator 24%, dinoprostone 28%, 41/0 gestational weeks) and fetal indication (13%, 28%, osmotic dilator, dinoprostone respectively; such as placental insufficiency, fetal growth restriction, oligohydramnios, polyhydramnions). All patients presented with an unfavorable cervix: the mean Bishop Score was 1.6 (±1.3) in the osmotic dilator group vs. 1.9 (±1.3) in the dinoprostone group.

Table 1: Baseline characteristics.

	Osmotic dilator n=104	Dinoprostone n=102	p overall
Maternal age, years	32.6 (4.78)	31.8 (5.72)	0.283
BMI pre-pregnancy, kg/m^2	26.1 (6.28)	26.6 (5.77)	0.586
Gravida	3.02 (1.34)	3.18 (1.33)	0.400
Para	1.38 (0.80)	1.35 (0.78)	0.842
No vaginal delivery	80 (77%)	79 (77.5%)	0.767
1 vaginal delivery	13 (12.5%)	15 (14.8%)	
≥2 vaginal deliveries	11 (10.5%)	8 (7.7%)	
Gestational weeks, days upon delivery	281 (7.64)	280 (8.26)	0.779
Indication for induction			0.620
Post-term pregnancy, n (%)	25 (24%)	29 (28%)	
Maternal indication, n (%)	66 (63%)	45 (44%)	
Fetal indication, n (%)	13 (13%)	28 (28%)	
Initial Bishop score	1.6 (1.3)	1.9 (1.3)	0.302

Data are presented as mean ± SD, or total number (percentage), BMI, body mass index.

Time from application to birth

The time period from application of the agent to onset of labor and time of birth was assessed (Table 2). Different time points were analysed. The time period from administration of the agent to onset of labor was significantly longer in the Dilapan-S® group compared to dinoprostone group with 37.9 vs. 20.7 h (mean, respectively, p=<0.001). Time from onset of labor to delivery was similar in both groups with 7.9 and 7.4 h (mean, Dilapan-S® group, dinoprostone group, respectively, p=0.758). Therefore, the period from application of the cervical ripening agent to onset of labor was longer in those who received the osmotic dilator. However, time from onset of labor to delivery was comparable.

Oxytocin augmentation/amniotomy

For further induction/labor augmentation, oxytocin was administered (Table 3). Patients receiving cervical ripening with Dilapan-S® required labor augmentation significantly more frequently with oxytocin in 76% (79) in comparison to 43.1% (44) in the dinoprostone group (p=<0.001). The rates of spontaneous rupture of membranes or amniotomy were similar in both groups (p=0.580).

Table 2: Time from application to delivery.

	Osmotic dilator n=104	Dinoprostone n=102	p overall
Time admission-onset/ labor, hours	37.9 (23.3)	20.7 (17.8)	<0.001
Time admission-delivery, hours	46.5 (24.9)	31.8 (24.0)	<0.001
Time onset labor-delivery, hours	7.93 (10.4)	7.44 (9.58)	0.758

Data are presented as mean (±SD).

Table 3: Induction of labor with oxytocin and amniotomy.

	Osmotic dilator n=104	Dinoprostone n=102	p overall
Labor augmentation with oxytocin	79 (76.0%)	44 (43.1%)	<0.001
Amniotomy	56 (53.8%)	50 (49.0%)	0.580
Spontaneous rupture of membranes	48 (46.2%)	52 (51.0%)	

Delivery mode

Overall, results concerning delivery mode were similar (p=0.603, Table 4). The cesarean section rate was 49.97% (44.2% during labor and delivery and 5.77% on request of the mother) in the osmotic dilator group vs. 48.02% (44.1 and 3.92%, respectively) in the dinoprostone group. 42.3% of patients delivered vaginally and 7.69% by ventouse. In those patients who required cervical ripening with dinoprostone 48% gave birth vaginally and 3.92% by ventouse.

Maternal outcome: uterine rupture vs. dehiscence

In our study cohort there was only one case of uterine rupture. A 32 year-old Gravida three Para one was induced with a total dosage of 3 mg dinoprostone at 40 gestational weeks due to oligohydramnios. After onset of labor she delivered the baby quickly within 4 h vaginally with an umbilical artery pH of 6.86, base excess –18.6 and an Apgar of 6/10/10 (see case 2, fetal outcome). Directly postpartum she started bleeding. In the ultrasound there was free fluid and the suspicion of uterine rupture, therefore a laparotomy was performed confirming the suspicion. The patient was suffering a high blood loss of 10 L and received an emergency hysterectomy as well as postoperative intensive care. She was discharged from the hospital 10 days after the delivery. In the osmotic dilator group there were no cases of uterine rupture but three cases of uterine dehiscence that were diagnosed during the RCS. In the dinoprostone group there was one case of uterine dehiscence. These cases were diagnosed during RCS, fetal and maternal outcome was otherwise uneventful in these cases. Uterine dehiscence, in contrast to uterine rupture, is defined as an incomplete division, not penetrating all layers of the uterus. Usually, uterine dehiscence is an occult finding in an asymptomatic patient [28].

Table 4: Illustrating the delivery mode, data in total (percentage).

	Osmotic dilator n=104	Dinoprostone n=102	p overall
Mode of delivery			0.603
Spontanous vaginal	44 (42.3%)	49 (48.0%)	
Ventouse	8 (7.69%)	4 (3.92%)	
Cesarean section, primary, w/o labor	6 (5.77%)	4 (3.92%)	
Cesarean section, secondary	46 (44.2%)	45 (44.1%)	

Fetal outcome

There were no significant differences concerning fetal outcome Tables 5 and 6. Analysing the Apgar score after 1, 5 and 10 min, fetal outcomes were very similar. No significant differences were found in average umbilical artery pH and Apgar scores. The lowest incidence of umbilical artery pH was found in the group of patients where dinoprostone was applied for cervical ripening, in this

Table 5: Apgar and pH outcomes, data as mean (±SD).

	Osmotic dilator n=104	Dinoprostone n=102	p overall
Apgar_1min	8.85 (0.73)	8.83 (1.18)	0.926
Apgar_5min	9.64 (0.59)	9.64 (0.59)	0.933
Apgar_10min	9.85 (0.41)	9.86 (0.45)	0.782
NapH	7.26 (0.07)	7.26 (0.09)	0.755
NaBE	–2.72 (3.49)	–4.13 (3.86)	0.014

Table 6: Four cases of peripartum asphyxia with a pH of lower than 7.10

<7.10		Osmotic dilator	Dinoprostone
Case 1		7.07 BE -7.4	
	Mode of delivery	Vaginally	
	Apgar	6/8/10	
	Birth weight	4110 g	
Case 2			6.86 BE -18.6
	Mode of delivery		Vaginally
	Apgar		6/10/10
	Birth weight		3470 g
Case 3			7.06 BE -10.6
	Mode of delivery		Vaginally
	Apgar		9/10/10
	Birth weight		3200 g
Case 4			7.08 BE -13
	Mode of delivery		Ventouse
	Apgar		6/9/10
	Birth weight		3540 g

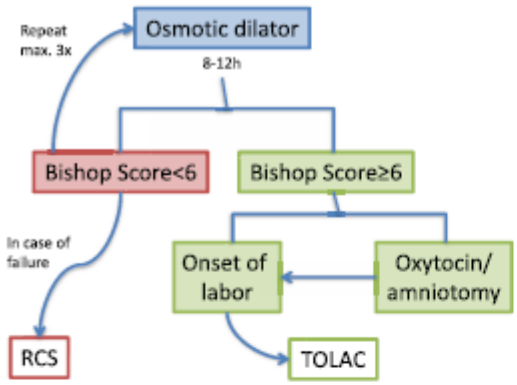

Figure 1: Flow-chart depicting the application of the osmotic dilator and subsequent steps depending on Bishop Score.

case due to uterine hyperstimulation (pH 6.86, base excess –18.6, vaginal delivery, Apgar 6/10/10). Overall, both groups had a similar proportion of umbilical artery pH lower than 7.20 (20.2 vs. 21.6%, Dilapan-S® group, dinoprostone group, respectively).

Discussion

With the cesarean section rate rising, trial of labor appears as a viable option to counteract this trend. Vaginal birth after cesarean can decrease the rates of short-term and long-term maternal and fetal complications [10]. TOLAC is a good option for influencing the overall rising CS rate, with a success rate of 80–60% leading to VBAC [16, 29, 30]. If induction of labor is required, the obstetrician's choice is limited as most pharmacological/mechanical agents prescribed (Prostaglandin, double balloon catheter) are not officially licensed for the usage in this particular group of patients. Moreover evidence on appropriate and safe options is very limited [31]. Legal consequences can be very harsh and therefore influence the physician in their decision in favor of the seemingly safer option, the RCS. This is why we are studying the application of an in-label device in patients with one prior cesarean section. As there is no comparative in-label agent available in this subgroup of patients, we had to compare the application with off-label prostaglandin from the past.

Principal findings

In this comparative study we were analysing 104 patients that received cervical ripening with the osmotic dilator to 102 patients that received prostaglandins (dinoprostone). The power analysis that was previously performed calculated group sample sizes of 92 and 92, achieving 80% power to detect non-inferiority. The two groups appear to be comparable with no significant differences between the two populations.

Mode of delivery

The overall success rate of VBAC is described as 60–80%, whereas women presenting with spontaneous onset of labor have the highest success rate [10, 13–16]. Recent studies have shown a prediction model to assess the success rate of vaginal delivery after cesarean using head circumference, subpubic angle and cervical length [32]. In addition, the indication for the CS prior to the current delivery has an impact on the success rate of TOLAC (e.g. breech, failure to progress in first or second stage of labor) [33]. Unfortunately, due to the small sample size, the indication for the prior CS was not extensively evaluated. This should be assessed in larger studies in the future.

Evidence concerning cervical ripening in women with one previous CS is limited. The American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynecologists (RCOG), and the French College of Gynecologists and Obstetricians (CNGOF) suggest in their bulletins the use of mechanical ripening agents, as there is no "negative" evidence associated to them. Furthermore, they do not recommend the application of PGE2 in this subgroup of patients [7, 10, 34]. Evidence on cervical ripening with the double-balloon catheter in TOLAC demonstrated a vaginal birth rate of 43.8–56.4% [35, 36]. In our study the VBAC rate was similar in both groups with 49.9 vs. 51.9% resembling the results from the double balloon catheter (p=0.602, osmotic dilator, dinoprostone, respectively). Notably the patients included into this study were at a gestational age of 41 weeks on average and had a very low Bishop Score of 1.5 (osmotic dilator group). Research has shown that post-term pregnancy in TOLAC has a decreased chance of VBAC [10].

Overall, when counseling a patient planning TOLAC and who presents with an indication for cervical ripening and labor induction, we can inform them that they have a 50% success rate on average.

Time period

The time period from first insertion or application to onset of labor was significantly longer in the osmotic dilator

group (p=0.005), which can be explained through the different mechanism of action of both agents. Interestingly, the time period was similar from onset of labor to delivery in both groups (p=0.7474). Cromi et al. observed a similar pattern with their study on the transcervical Foley vs. prostaglandins for cervical ripening: the mechanical device had a lower rate of vaginal birth within 24 h compared to prostaglandins, but the same overall chance of vaginal birth [37]. A longer interval from cervical ripening to active phase of labor has been described in patients with a previous CS when comparing to nulliparous women [38]. Additionally, a mechanical agent that works slower and therefore prevents uterine hyperstimulation decreasing the risk of uterine rupture is an aspect that is deliberately desired in TOLAC.

Oxytocin and amniotomy

A current meta-analysis revealed a correlation between oxytocin use in TOLAC and risk of uterine rupture [16]. The uterine rupture risk is estimated to be 1% in oxytocin and to be dose-dependent [7]. Oxytocin ought not to be routinely used in TOLAC and if it is, should be maintained at the lowest concentration to sustain contractions. In comparison, the application of vaginal prostaglandins increases the uterine rupture risk by about 2%, therefore the usage of prostaglandin in induction of labor in this subgroup is not generally recommended and should be considered carefully [7]. In our analysis, we found higher rates of oxytocin application and/or amniotomy in the group of the osmotic dilator. This can be explained through the mechanical mode of action of the osmotic dilator in comparison to the vaginal application of dinoprostone that acts there continuously. In our osmotic dilator protocol, we recommend performing artificial rupture of membranes after a maximum of 2 h of oxytocin administration. Research shows that after cervical ripening, routine early amniotomy shortens the interval from induction to delivery and does not increase the risk of secondary RCS [39].

Safety

Recent studies showed that uterine rupture occurs at a frequency of 0.2% in all patients attempting vaginal birth after having one previous cesarean section [40, 41]. The risk of uterine rupture is dependent on different aspects: the type of uterine suture (single stitches vs. continuous stitching), excessive diathermy, wound healing, and other conditions [27]. There is evidence that induction of labor and cervical ripening impose different risks on uterine rupture and consequently on maternal and fetal health. The risk of uterine rupture appears to be lowest with oxytocin but dependent on dosage, the risk increasing with the application of prostaglandins [7, 10, 16]. There is little evidence on mechanical devices. Studies with the double balloon catheter revealed a very low uterine rupture rate of 1.2% (18/1447) [36]. In this study we observed one uterine rupture with a substantial maternal and fetal morbidity (fetal asphyxia and emergency hysterectomy) in the dinoprostone group. There were three cases of uterine dehiscence in the osmotic dilator group and one case in the dinoprostone group. These cases were diagnosed by chance during the RCS und both maternal and fetal outcome were uneventful. Due to the small sample size (n=104 and 102) further studies with larger cohorts need to be performed in this critical safety aspect. Additionally, the aspect of uterine hyperstimulation should be further analysed in larger cohorts. We suspect a lower incidence of uterine hyperstimulation in the osmotic dilator group because of its slower way of acting, e.g. longer interval from insertion to onset of labor in this group.

Fetal outcome was comparable in both groups with no significant differences.

Critical assessment of this study and future outlook

Here we are prospectively comparing the application of the osmotic dilator to the off-label and currently not recommended usage of dinoprostone in patients with one prior CS (historic group). We were able to show that cervical ripening in this subgroup with a low Bishop Score and therefore a higher risk of secondary RCS and uterine rupture had a success rate of vaginal delivery in 49.9 vs. 51.9% (osmotic dilator, dinoprostone, respectively). This data is analogous to the evidence in literature with a vaginal birth rate of 43.8–56.4% and our own previous publications [24, 35, 36]. Still, the number of women included into this study is too small to facilitate a more comprehensive analysis.

Overall, this comparative analysis shows promising results on the efficiency and safety of the osmotic dilator in cervical ripening before TOLAC and underlines the current recommendations from the ACOG, RCOG and CNGOF. The results are limited by the fact that the control group consists of a retrospective series.

Conclusions

To date there is no published study with a randomized setting analysing the application of the osmotic dilator in women with one previous CS. This study concludes that the osmotic dilator is a viable option for cervical ripening in women who had a previous cesarean section. It is as effective in mode of delivery and actual time from onset of labor to delivery as prostaglandins.

In women with one previous CS we want to be careful with the administration of drugs that are known to implement a higher risk of uterine hyperstimulation and pathological fetal heart rate tracing. With the osmotic dilator and its mechanical mode of action it is understandable that it acts slower than prostaglandins and has a higher need for well-controllable titration of Oxytocin and amniotomy.

In the future we would like to initiate an international randomized controlled study on the application of the osmotic dilator vs balloon catheter. We hope that eventually more women are provided with the opportunity of VBAC and that the overall cesarean section rate can be lowered.

Additionally, the osmotic dilator appears to be a safe and viable option in outpatient cervical ripening and could therefore reduce hospital stays and socioeconomic costs. Furthermore, in the face of a worldwide pandemic, outpatient cervical ripening in a low risk cohort leads to less individual contacts and a smaller likelihood to get infected or spread SARS-CoV-2.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: Prior to the analysis, we requested an ethics committee meeting and received approval from the Ethics Committee of the Ärztekammer, Berlin (September 20th, 2016; Eth-37/16).

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2.3. Glucose levels of the oral glucose tolerance test (oGTT) can predict adverse pregnancy outcomes in women with gestational diabetes (GDM)

Der GDM ist eine Glukosestoffwechselstörung, die in der Schwangerschaft diagnostiziert wird. Es handelt sich um eine häufige Schwangerschaftskomplikation mit einer Prävalenz von 8,5 % (2021) (67, 68). In Deutschland erfolgt das GDM-Screening mit einem 50-g-oGTT. Sollte der Ein-Stunden-Wert ≥135 mg/dl und somit pathologisch sein, folgt der 75-g-oGTT (Grenzwerte ≥92, ≥180, ≥153 mg/dl) (61). Es wird vermutet, dass bei Frauen mit GDM verschiedene metabolische Typen unterschieden werden können (69). Diese metabolischen Typen können mit verschiedenen Komplikationen assoziiert sein, was nahelegt, dass die Betreuung der Schwangeren personalisiert erfolgen sollte.

In dieser Untersuchung wurden die geburtsmedizinischen sowie perinatalen und neonatalen Daten von 1664 Frauen retrospektiv analysiert. Unter anderem wurden die Ergebnisse des 75-g-oGTT kategorisiert in isoliert erhöhte Nüchternglukose (Isolated Fasting Hyperglycemia = GDM-IFH), isoliert erhöhte Postprandialglukose (Isolated Post-Load Hyperglycemia = GDM-IPH) und kombiniert erhöhte Glukosewerte (Combined Hyperglycemia = GDM-CH).

Die Ergebnisse der Arbeit zeigen, dass Frauen aus der GDM-IFH und GDM-CH einen höheren präkonzeptionellen BMI aufwiesen und häufiger Insulin benötigten, um den GDM zu therapieren (P Wert < 0,001). Frauen, die als GDM-IFH-Typ kategorisiert wurden, hatten ein höheres Risiko, ihr Neugeborenes per Kaiserschnitt auf die Welt zu bringen (*p*-Wert = 0,047). Die Kinder von Frauen der Typen GDM-IFH und GDM-CH wiesen ein deutlich höheres Geburtsgewicht auf (*p*-Wert < 0,001) und zeigten ein höheres Risiko, makrosom zu sein (Large for Gestational Age = LGA) (*p*-Wert = 0,004). Im Kontrast dazu waren die Neugeborenen von Frauen des GDM-IPH-Typs häufiger zart mit einem Geburtsgewicht unter der zehnten Perzentile des Wachstumsdiagramms (*p*Wert = 0,027).

Die Untersuchung konnte zeigen, dass bei Schwangeren mit einem GDM verschiedene metabolische Typen zu identifizieren sind, die direkt in Zusammenhang mit dem Schwangerschaftsverlauf und dem perinatalen Outcome stehen. Weitere Untersuchungen dazu ergaben, dass zusätzlich das mütterliche Alter eine Rolle spielt und in direktem Zusammenhang mit einem ungünstigeren Schwangerschaftsverlauf steht (44).

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Glucose Levels of the Oral Glucose Tolerance Test (oGTT) Can Predict Adverse Pregnancy Outcomes in Women with Gestational Diabetes (GDM)

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Abstract: Objectives and Background: Gestational diabetes (GDM) is a common pregnancy complication defined as a glucose intolerance diagnosis during pregnancy. GDM is strongly associated with adverse fetal and maternal outcomes. In Germany, to screen and diagnose GDM we use a 1 h 50 g oGCT (oral glucose challenge test) followed by a 2 h 75 g oGTT if the first was pathological. This analysis examines the correlation of 75 g oGTT glucose levels and fetomaternal outcome. Methods: Data from 1664 patients from a gestational diabetes consultation clinic at the Charité University Hospital in Berlin, Germany, were analyzed retrospectively from 2015 to 2022. The 75 g oGTT blood glucose levels were categorized into isolated fasting hyperglycemia (GDM-IFH), isolated post-load hyperglycemia (GDM-IPH) and combined hyperglycemia (GDM-CH), using the levels of the fasting, 1 h and 2 h values, after glucose application. These subtypes were compared based on their baseline characteristics as well as fetal and maternal outcome. Results: GDM-IFH and GDM-CH women displayed higher pre-conceptional BMI and required insulin therapy more frequently ($p < 0.001$). The GDM-IFH group was at higher risk of having a primary cesarean section ($p = 0.047$), while GDM-IPH women were significantly more likely to have an emergent cesarean section ($p = 0.013$). The offspring of GDM-IFH and GDM-CH women were born with a significantly higher mean birthweight ($p < 0.001$) and birth weight percentiles ($p < 0.001$) and were at increased risk of being large for gestational age (LGA) ($p = 0.004$). Women from the GDM-IPH group delivered significantly more neonates who were small for gestational age ($p = 0.027$) or with low fetal weight <30th percentile ($p = 0.003$). Conclusion: This analysis shows a strong association between the glucose response pattern in the 75 g oGTT and adverse perinatal fetomaternal outcome. The differences among the subgroups, specifically concerning insulin therapy, mode of delivery and fetal growth, suggest an individualized approach to prenatal care after a GDM diagnosis.

Keywords: oGTT; oral glucose tolerance test; gestational diabetes; GDM; cesarean section

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1. Introduction

Gestational diabetes mellitus (GDM) is a common complication during pregnancy. In Germany, the incidence of GDM rose from 4.6% of all hospital deliveries in 2013 to 6.8% in 2018 [1]. GDM is defined as an impairment of glucose tolerance that has been diagnosed for the first time during pregnancy [2]. With its prevalence rising, and its well-known associations with other various pregnancy complications such as pre-eclampsia, cesarean section (CS), macrosomia, shoulder dystocia, childbirth injury, postpartum hemorrhage or premature birth, understanding GDM fully is key to improve prenatal care and minimize the risks for mother and child [3–7]. GDM is still, generally, treated as a homogenous disease during pregnancy, although research indicates that a more differentiated approach might be needed, as phenotypical subtypes of the condition seem to be associated with different perinatal outcomes. A possible approach that has been suggested is to focus

on the extent of insulin sensitivity and insulin secretion impairment or to differentiate between the two [8–11]. Another, possibly more practicable, approach is to differentiate GDM subtypes based on the glucose levels observed in the three-point 75 g oral glucose tolerance test (oGTT), which is conducted in the late second to early third trimester of pregnancy and comprises fasting blood glucose measurements, one and two hours after the ingestion of a 75 g glucose solution (Figure 1) [2]. These measurements are widely available through the prenatal file and are, therefore, easy to access. The HAPO study demonstrated an association of maternal plasma glucose levels with large for gestational age (LGA) offspring, primary CS, shoulder dystocia or birth injury, pre-eclampsia and other adverse outcomes [12]. Therefore, the correlation of 75 g oGTT glucose values and fetomaternal outcome has been the subject of several studies [5,13–15]. The aim of our study is to corroborate and add evidence to the recent findings by assessing the characteristics of GDM subtypes (isolated fasting hyperglycæmia = GDM-IFH, isolated post-load hyperglycæmia = GDM-IPH, combined hyperglycæmia = CH based on oGTT glucose values) and their respective risk of adverse maternal and fetal outcomes.

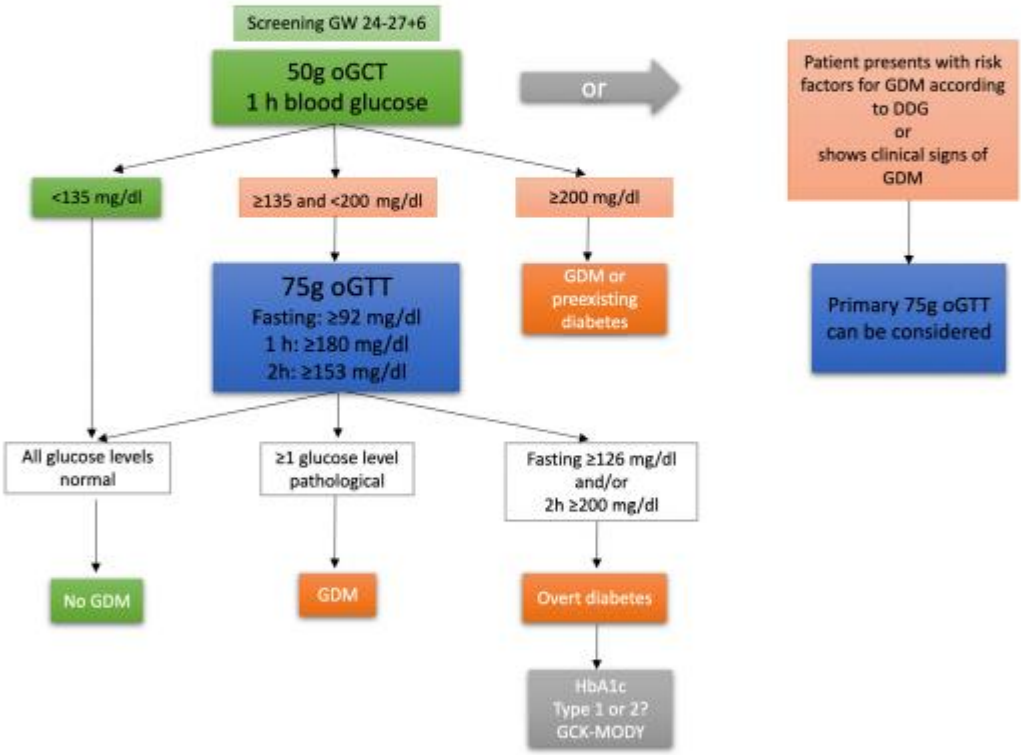


Figure 1. Screening and diagnostic process of GDM in Germany. Initially a 50 g oral glucose challenge test (oGCT) is offered to every pregnant woman between 24 and 28 gestational weeks (GW). Depending on the blood glucose level, further testing for GDM is required. In women with risk factors for GDM according to the Deutsche Diabetes Gesellschaft (DDG) or signs of GDM, a 75 g oral glucose tolerance test (oGTT) as a first-line diagnostic test is possible.

2. Materials and Methods

Obstetric data from 3123 pregnant women visiting an expert gestational diabetes consultation clinic at Charité University Hospital, from January 2015 to September 2022, were collected and analyzed anonymously. The Charité University Hospital is a tertiary perinatal center in the metropole region of Berlin, Germany. A total of 1664 patients were eligible

for the analysis (Figure 2). The patients were screened and diagnosed through the 75 g oGTT and in case of pathological results were referred to our consultation clinic. Inclusion criteria were women ≥18 years with singleton pregnancies who were screened prior with a pathological glucose response in the 75 g oGTT and were subsequently diagnosed with GDM. The gestational week (GW) at the time of the pathological 75 g oGTT did not affect inclusion. High-risk patients who received early screening (before 24 GW) were included. Only women who delivered their babies at Charité University Hospital were eligible for the analysis. Exclusion criteria were multiple pregnancies, age < 18 years, missing or incomplete oGTT data, missing perinatal data and inconclusive documentation of GDM diagnosis. The oGTT data were considered incomplete if at least one glucose measurement of the three-point 75 g oGTT was missing and subsequently the categorization into one of the subtypes was not possible. Women who were diagnosed through random elevated blood glucose levels were excluded as well. Patients were categorized into three different groups using the three blood glucose values from the 75 g oGTT. Thresholds for pathological glucose levels were ≥92 mg/dL (5.1 mmol/L) fasting, ≥180 mg/dL (10 mmol/L) one hour after glucose application and ≥153 mg/dL (8.5 mmol/L) two hours after, according to IADPSG criteria [16]. An elevation in fasting glucose only, which was measured immediately before the application of the glucose solution, was considered isolated fasting hyperglycemia (GDM-IFH). If just one or both postprandial glucose values were elevated, this was considered isolated post-load hyperglycemia (GDM-IPH) and an elevation in fasting glucose and at least one of the postprandial glucose values was categorized as combined hyperglycemia (GDM-CH). The primary aim of the analysis was to assess the likelihood of delivering via cesarean section based on the glucose values of the 75 g oGTT. The secondary objective was to analyze maternal and fetal outcome parameters, such as vaginal operative birth, shoulder dystocia, perineal tear grade 3° and the need for episiotomy, blood loss and postpartum bleeding, and pre-eclampsia. Fetal outcomes included gestational age at delivery, birth weight and percentiles, fetal growth abnormalities such as intrauterine growth retardation (IUGR), small for gestational age (SGA), LGA (defined as growth ≥ 95th percentile) and low fetal weight (defined as growth < 30th percentile), premature delivery before 37 GW, intrauterine fetal demise (IUFD) and the need for intensive neonatal care admission after delivery. Cord pH levels and base excess were evaluated.

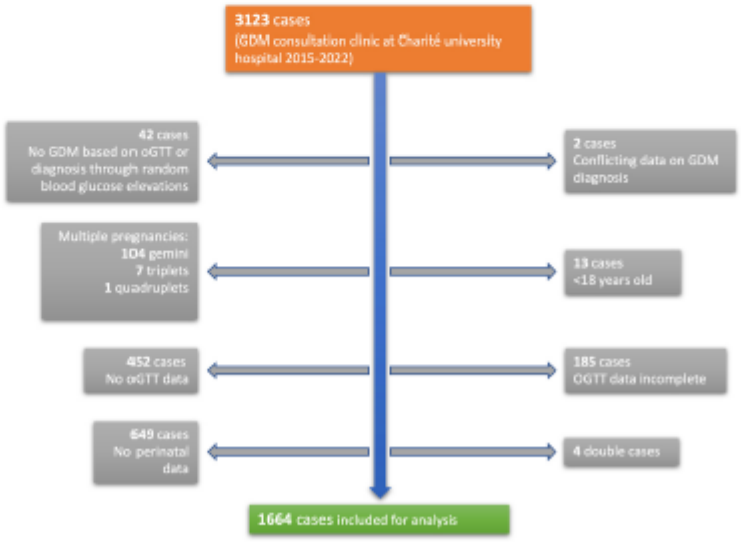


Figure 2. Obstetric data from 3123 pregnant women were collected and analyzed anonymously. A total of 1664 cases were eligible for analysis.

An analysis of the study population's underlying characteristics was conducted regarding maternal age, gravidity and parity, pre-conceptional BMI and the previous diagnostic process including GW at first presentation, the 50 g oGCT and the 75 g oGTT. Gravidity and parity were assessed as continuous as well as categorical variables (gravida 1, 2 and ≥3; nullipara vs. ≥primipara and para 0, 1, 2, ≥3).

This study received ethical approval from the ethics committee of Charité University Hospital on 6 February 2023 (EA2/255/22).

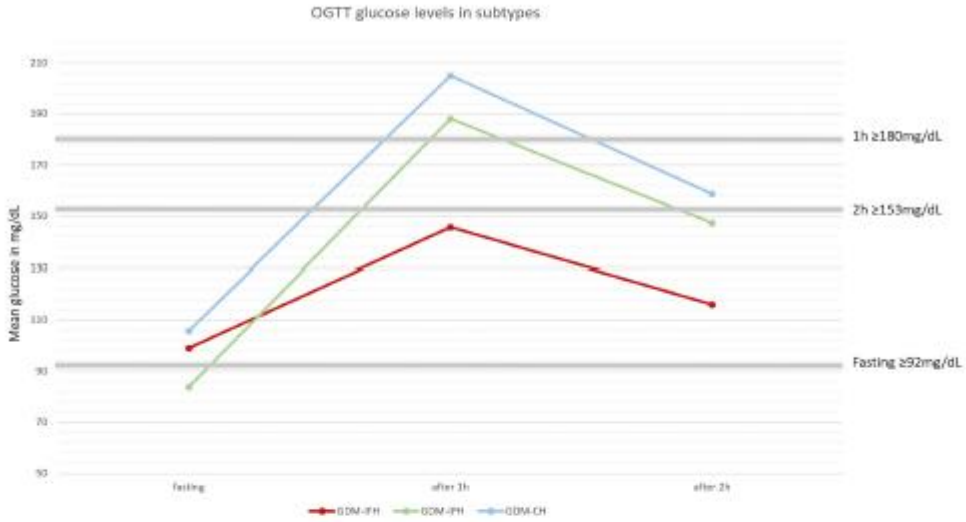
Data analysis was performed using SPSS Statistics by IBM (version 28.0.1.0) (Armonk, New York, United States of America). Categorical variables were compared among the subgroups using chi-square-tests and binomial logistic regression, and numbers and percentages were reported. Binomial logistic regression was conducted for outcome variables which showed significant differences among the subgroups and included subtype (categorical), pre-conceptional BMI (<18.5 = underweight, 18.5–23.9 = normal weight, 24–27.9 = overweight, 28–31.9 = obese, ≥32 = severely obese), age as a continuous variable and parity (nullipara vs. ≥primipara) as co-variates. Odds ratios and 95% confidence intervals were calculated and reported. Metric variables were compared using one-way ANOVA with subsequent post-hoc-analysis (Tukey and Games–Howell) and mean and standard deviation (SD) were reported. Results were considered statistically significant if the p-value was <0.05.

3. Results

3.1. Baseline Characteristics

Of the 1664 patients, 553 were classified as GDM-IFH (33.2%), 418 as GDM-IPH (25.1%) and 693 as GDM-CH (41.6%) (Figure 1). Mothers from the GDM-IFH group were, on average, significantly younger (IFH: 31.89, IPH: 32.62, CH: 32.70, $p = 0.024$). Mean gravidity (IFH: 2.88, IPH: 2.92, CH: 3.32, $p < 0.001$) and parity (IFH: 1.31, IPH: 1.26, CH: 1.69, $p < 0.001$) were significantly higher in the GDM-CH group. The analysis of gravidity and parity as categorical variables revealed that among all subtypes, multigravidity (gravida ≥ 3: IFH: 48.3%, IPH: 46.9%, CH: 59.8%, $p < 0.001$) was significantly more common than gravida 1 (IFH: 22.8%, IPH: 27.8%, CH: 17.8%) or 2 (IFH: 28.9%, IPH: 25.4%, CH: 22.4%). The rate of nulliparous women was significantly higher in the GDM-IPH group (IFH: 33.8%, IPH: 39.7%, CH: 25.0%, $p < 0.001$). GDM-CH women had the highest rate of pluriparity (para ≥ 3: IFH: 15.6%, IPH: 15.6%, CH: 26.2%). Primiparity and biparity were similarly common when comparing the subtypes (IFH: 32.2%, IPH: 26.6%, CH: 27.8% and IFH: 18.4%, IPH: 18.2%, CH: 21.0%, respectively). The pre-conceptional BMI differed significantly between all the subgroups: GDM-IPH women displayed the lowest mean BMI and GDM-CH women the highest (IFH: 28.63, IPH: 26.10, CH: 29.69, $p < 0.001$). The 50 g oGCT was performed on average at 26 GW, with no significant difference between the groups (IFH: 25.62 GW, IPH: 25.89 GW, CH: 25.89 GW, $p = 0.362$). The GDM-IFH group was less likely to receive the 50 g oGCT before the 75 g oGTT than the other subgroups (IFH: 43.9%, IPH: 60.3%, CH: 59.2%, $p < 0.001$) and less likely to show a pathological glucose response in the test (IFH: 85.7%, IPH: 93.4%, CH: 93.9%, $p < 0.001$). Mean glucose levels in the 50 g oGCT were 144.75 mg/dL (8.03 mmol/L) in the GDM-IFH, 157.69 mg/dL (8.75 mmol/L) in the GDM-IPH and 166.37 mg/dL (9.23 mmol/L) in the GDM-CH group ($p < 0.001$). Women with GDM-IFH received the 75 g oGTT earlier than women in the GDM-IPH or GDM-CH groups (mean: IFH: 25.78 GW, IPH: 27.23 GW, CH: 26.53 GW, $p < 0.001$). In the GDM-IFH and GDM-CH groups the 75 g oGTT was performed before 24 GW more often than in the GDM-IPH group (13.2%, 11.8% vs. 7.2%; $p = 0.009$). Mean 75 g oGTT glucose levels before glucose intake, 1 h after and 2 h after, were 99.02 mg/dL (5.50 mmol/L), 145.63 mg/dL (8.08 mmol/L) and 116.16 mg/dL (6.45 mmol/L) in women with GDM-IFH, 83.77 mg/dL (4.65 mmol/L), 188.11 mg/dL (10.44 mmol/L) and 147.28 mg/dL (8.17 mmol/L) in women with GDM-IPH and 105.84 mg/dL (5.87 mmol/L), 204.98 mg/dL (11.38 mmol/L) and 158.80 mg/dL (8.81 mmol/L) in women with GDM-CH, respectively, (Figure 3). The mean initial presentation at the GDM consultation clinic was at 31 GW (IFH: 30.22 GW,

IPH: 30.72 GW, CH: 30.39 GW, $p = 0.270$). A complete overview of the results is provided in Table 1.



Note: Threshold according to IADPSG consensus. Fasting ≥92mg/dL, 1h ≥180mg/dL, 2h ≥153mg/dL

Figure 3. Attributes of each subtype: Isolated fasting hyperglycemia (GDM-IFH), isolated postprandial hyperglycemia (GDM-IPH), combined hyperglycemia (GDM-CH). Thresholds for pathological glucose levels were ≥92 mg/dL (5.1 mmol/L) fasting, ≥180 mg/dL (10 mmol/L) one hour after glucose application and ≥153 mg/dL (8.5 mmol/L) two hours after [2].

Table 1. Baseline characteristics. Baseline characteristics on maternal age, pregnancy history, BMI, glucose screening and screening results.

		Subtype											
		GDM-IFH (n = 553)				GDM-IPH (n = 418)				GDM-CH (n = 693)			
		Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%
Maternal age		31.89$_a$	5.78			32.62$_b$	5.37			32.70$_b$	5.40		
Gravida		2.88$_a$	1.81			2.92$_a$	2.06			3.32$_b$	1.99		
Para		1.31$_a$	1.44			1.26$_a$	1.53			1.69$_b$	1.52		
Parity	Nullipara			187$_a$	33.8%			166$_a$	39.7%			173$_b$	25.0%
	≥Primipara			366$_a$	66.2%			252$_a$	60.3%			518$_b$	75.0%
Preconceptional BMI		28, 63$_a$	6,46			26, 10$_b$	5,33			29, 69$_c$	6, 33		
50 g oGCT	yes			243$_a$	43.9%			252$_b$	60.3%			410$_b$	59.2%
	no			310$_a$	56.1%			166$_b$	39.7%			283$_b$	40.8%
GW at 50 g oGCT		25, 62$_a$	2.18			25, 89$_a$	2.11			25, 85$_a$	2.38		
Glucose 50 g oGCT in mg/dL		144, 75$_a$	18.67			157, 69$_b$	21.71			166, 37$_c$	30.95		
50 g oGCT ≥ 135 mg/dL	yes			198$_a$	85.7%			225$_b$	93.4%			368$_b$	93.9%
	no			33$_a$	14.3%			16$_b$	6.6%			24$_b$	6.1%
GW at 75 g oGTT		25, 78$_a$	4.67			27, 23$_b$	3.76			26, 53$_c$	4.27		
75 g oGTT	before GW 24+0			73$_a$	13.2%			30$_b$	7.2%			82$_a$	11.8%
	after GW 24+0			480$_a$	86.8%			388$_b$	92.8%			611$_a$	88.2%
Fasting glucose in mg/dL		99, 02$_a$	8.35			83, 77$_b$	5.97			105, 84$_c$	14.95		
Glucose after 1 h in mg/dL		145, 63$_a$	22.63			188, 11$_b$	22.31			204, 98$_c$	32.01		
Glucose after 2 h in mg/dL		116, 16$_a$	19.93			147, 28$_b$	31.28			158, 80$_c$	36.67		
GW at first presentation		30, 22$_a$	4.76			30, 72$_a$	4.42			30, 39$_a$	4.97		

Note: Values in the same row that are marked with different subscripts (a,b and c) differ significantly with a p-value < 0.05.

3.2. Maternal Outcome

As provided in Table 2, the GDM-IFH group displayed the highest mean weight gain (IFH: 12.17 kg, IPH: 11.24 kg, CH: 10.90 kg, $p = 0.008$). GDM-IFH (17.5%, OR 1.946 [1.277–2.967], $p = 0.002$) as well as GDM-CH women were more likely to require insulin therapy (34.2%, OR 4.317 [2.915–6.392], $p < 0.001$) compared to GDM-IPH women (8.9%). GDM-CH patients had a higher likelihood of receiving insulin therapy (OR 2.218 [1.674–2.937], $p < 0.001$) compared to GDM-IFH. The use of long-acting insulin only was significantly more common in the GDM-IFH and GDM-CH groups (IFH: 13.0%, IPH: 5.3%, CH: 19.5%, $p < 0.001$) and the rate of combined insulin therapy was higher in the GDM-CH group (IFH: 3.8%, IPH: 1.4%, CH: 12.8%, $p < 0.001$). Two patients received treatment with metformin in combination with insulin.

Table 2. Maternal outcome. Maternal outcome regarding GDM therapy, pregnancy complications and delivery mode and birth complications.

		Subtype											
		GDM-IFH (n = 553)				GDM-IPH (n = 418)				GDM-CH (n = 693)			
		Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%
Weight gain		12.17$_a$	7.05			11.24$_b$	6.23			10.90$_b$	6.43		
Insulin	long acting insulin only			72$_a$	13.0%			22$_b$	5.3%			135$_c$	19.5%
	combined insulin			21$_a$	3.8%			6$_b$	1.4%			89$_c$	12.8%
	short acting insulin only			4$_a$	0.7%			9$_a$	2.2%			13$_a$	1.9%
	no			456$_a$	82.5%			381$_b$	91.1%			456$_c$	65.8%
Metformin	yes			1$_a$	0.2%			0^2	0.0%			1$_a$	0.1%
	no			552$_a$	99.8%			418^2	100.0%			692$_a$	99.9%
Preeclampsia	yes			18$_a$	3.3%			7$_a$	1.7%			26$_a$	3.8%
	no			535$_a$	96.7%			411$_a$	98.3%			667$_a$	96.2%
HELLP	yes			2$_a$	0.4%			1$_a$	0.2%			1$_a$	0.1%
	no			551$_a$	99.6%			417$_a$	99.8%			692$_a$	99.9%
Delivery mode	Vaginal			279$_a$	50.5%			200$_a$	47.8%			355$_a$	51.3%
	Vacuum extraction			45$_{a,b}$	8.1%			41$_a$	9.8%			38$_b$	5.5%
	Primary CS			137$_a$	24.8%			76$_b$	18.2%			149$_{a,b}$	21.5%
	Emergent CS			92$_a$	16.6%			100$_b$	23.9%			150$_b$	21.7%
	Forceps extraction			0	0.0%			1	0.2%			0	0.0%
Shoulder dystocia	yes			4$_a$	1.2%			0	0.0%			8$_a$	2.0%
	no			320$_a$	98.8%			242	100.0%			385$_a$	98.0%
Perineal tear	yes			114$_a$	35.2%			95$_a$	39.3%			133$_a$	33.8%
	no			210$_a$	64.8%			147$_a$	60.7%			260$_a$	66.2%
Third degree perineal tear	yes			6$_a$	1.9%			3$_a$	1.2%			4$_a$	1.0%
	no			318$_a$	98.1%			239$_a$	98.8%			389$_a$	99.0%
Episiotomy	yes			27$_a$	8.3%			28$_a$	11.6%			35$_a$	8.9%
	no			297$_a$	91.7%			214$_a$	88.4%			358$_a$	91.1%
Blood loss in mL		443$_a$	287			450$_a$	373			433$_a$	257		
Blood loss ≥1000 mL	yes			26$_a$	4.8%			18$_a$	4.5%			28$_a$	4.2%
	no			516$_a$	95.2%			385$_a$	95.5%			645$_a$	95.8%
Blood loss ≥1500 mL	yes			10$_a$	1.8%			9$_a$	2.2%			8$_a$	1.2%
	no			532$_a$	98.2%			394$_a$	97.8%			665$_a$	98.8%
Postpartum bleeding	yes			27$_a$	4.9%			22$_a$	5.3%			38$_a$	5.5%
	no			526$_a$	95.1%			396$_a$	94.7%			655$_a$	94.5%

Note: Values in the same row that are marked with different subscripts (a, b and c) differ significantly with a p-value < 0.05.

The analysis showed no significant difference between rates of CS (primary and emergent, $p = 0.811$). However, there was a significant difference on primary and emergent CS specifically. GDM-IFH women were most likely to deliver via planned primary CS compared to GDM-IPH (IFH: 24.8%, IPH: 18.2%, CH: 21.5%, $p = 0.047$). The odds of delivering via primary CS were significantly increased only in GDM-IFH women (OR 1.376 [1.042–1.815], $p = 0.024$) vs. GDM-CH patients. Women categorized as GDM-IPH (23.9%, OR 1.643 [1.173–2.302], $p = 0.004$) or GDM-CH (21.7%, OR 1.48 [1.094–2.003], $p = 0.011$)

were at higher risk of an emergent CS compared to GDM-IFH women (16.6%). The rate of vaginal operative delivery differed significantly with 10% in GDM-IPH patients vs. 5.5% in GDM-CH patients (IFH: 8.1%, $p = 0.016$). There were no significant differences concerning the rates of shoulder dystocia (IFH: 1.2%, IPH: 0.0%, CH: 2.0%, $p = 0.081$), episiotomy (IFH: 8.3%, IPH: 11.6%, CH: 8.9%, $p = 0.389$), third degree perineal tear (IFH: 1.9%, IPH: 1.2%, CH: 1.0%, $p = 0.620$), pre-eclampsia (IFH: 3.3%, IPH: 1.7%, CH: 3.8%, $p = 0.143$) and HELLP syndrome (IFH: 0.4%, IPH: 0.2%, CH: 0.1%, $p = 0.739$). The analysis of blood loss as a continuous variable showed no significant difference ($p = 0.643$), as well as the incidence of blood loss $\geq$ 1000 mL ($p = 0.867$) and $\geq$1500 mL ($p = 0.400$). The risk of postpartum bleeding was similar throughout the subgroups ($p = 0.893$).

3.3. Fetal Outcome

The distribution of the fetus's sex did not differ significantly between the groups ($p = 0.760$). The mean gestational age at delivery was slightly higher in the GDM-IFH group than in the GDM-CH group (IFH: 39.70 GW, IPH: 39.51 GW, CH: 39.41 GW, $p = 0.008$). The rates of premature delivery before 37 GW were similar among the subtypes ($p = 0.054$). APGAR scores at 1 min ($p = 0.088$), 5 min ($p = 0.110$) and 10 min after delivery ($p = 0.061$), arterial cord pH values ($p = 0.446$) and base excess ($p = 0.906$) did not differ significantly among the subgroups. Neonates of GDM-IFH and GDM-CH mothers displayed a significantly higher mean birthweight (IFH: 3470.71 g, IPH: 3327.59 g, CH: 3460.21 g, $p < 0.001$) as well as birth weight percentiles (IFH: 54.68, IPH: 49.43, CH: 57.51, $p < 0.001$) compared to neonates of GDM-IPH women. GDM-IFH (12.3%, OR 1.657 [1.020–2.692], $p = 0.041$) and GDM-CH women (13.5%, OR 1.671 [1.046–2.668], $p = 0.032$) were at higher risk of delivering neonates that were LGA compared to GDM-IPH (6.5%). The SGA rate was significantly higher among GDM-IPH women (IFH: 7.6%, IPH: 11.5%, CH: 7.1%, $p = 0.027$). In the logistic regression analysis, SGA did not reach statistical significance. However, GDM-IPH women (30.7%, OR 1.379 [1.029–1.847], $p = 0.031$) displayed an association with low fetal weight (<30th percentile) in comparison to GDM-CH women (21.6%, IFH: 26.3%). There was no significant difference in neonatal intensive care admission ($p = 0.086$) and the rate of IUFD ($p = 0.104$) (Table 3).

Table 3. Fetal outcome. Fetal outcome regarding gestational age at delivery, birthweight, Apgar and cord blood pH.

		Subtype											
		GDM-IFH (n = 553)				GDM-IPH (n = 418)				GDM-CH (n = 693)			
n		n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD
Sex of fetus	male	305_a	55.2%			234_a	56.3%			372_a	54.0%		
	female	248_a	44.8%			182_a	43.8%			317_a	46.0%		
GW at delivery				39.70_a	1.50			$39.51_{a,b}$	2.08			39.41_b	1.92
Prematurity <37 GW	yes	16_a	2.9%			25_a	6.0%			35_a	5.1%		
	no	537_a	97.1%			393_a	94.0%			657_a	94.9%		
Birthweight				3470.71$_a$	556.88			3327.59$_b$	609.55			3460.21$_a$	605.72
Birthweight percentile				54.68_a	30.16			49.43_b	29.52			57.51_a	29.65
IUGR	yes	9_a	1.6%			13_a	3.1%			9_a	1.3%		
	no	543_a	98.4%			404_a	96.9%			682_a	98.7%		
SGA	yes	42_a	7.6%			48_b	11.5%			49_a	7.1%		
	no	510_a	92.4%			369_b	88.5%			642_a	92.9%		
Low fetal weight	yes	$145_{a,b}$	26.3%			128_a	30.7%			149_b	21.6%		
	no	$407_{a,b}$	73.7%			289_a	69.3%			542_b	78.4%		
LGA	yes	68_a	12.3%			27_b	6.5%			93_a	13.5%		
	no	484_a	87.7%			390_b	93.5%			598_a	86.5%		
APGAR at 1 min				8.62_a	1.20			8.64_a	1.03			8.49_a	1.38
APGAR at 5 min				9.56_a	0.91			9.49_a	0.96			9.43_a	1.17
APGAR at 10 min				9.81_a	0.66			9.75_a	0.77			9.70_a	1.01
Cord pH				7.24_a	0.07			7.24_a	0.07			7.24_a	.07
Base excess				-4.44_a	2.96			-4.38_a	3.25			-4.36_a	3.24
NICU	yes	28_a	5.1%			36_a	8.6%			45_a	6.5%		
	no	525_a	94.9%			382_a	91.4%			648_a	93.5%		
IUFD	yes	1_a	0.2%			0	0.0%			5_a	0.7%		
	no	552_a	99.8%			418	100.0%			687_a	99.3%		

Values in the same row that are marked with different subscripts (a, b and c) differ significantly with a p-value < 0.05.

3.4. Effects of Covariates on Fetomaternal Outcome

In the logistic regression model, not only the three 75 g oGTT subtypes were associated with fetomaternal outcome. In particular, parity and pre-conceptional BMI seemed to significantly affect the perinatal outcomes. Nulliparous women displayed smaller odds of primary CS (OR 0.435 [0.320–0.593], $p < 0.001$), but were at higher risk of delivering via emergent CS (OR 3.534 [2.700–4.625], $p < 0.001$). Their likelihood of operative vaginal delivery was higher as well (OR 6.353 [4.100–9.843], $p < 0.001$). Nulliparity increased the odds of delivering offspring that had low fetal weight (OR 1.583 [1.238–2.025], $p < 0.001$) or was SGA (OR 2.155 [1.484–3.129], $p < 0.001$), while it reduced the odds of delivering LGA neonates (OR 0.548 [0.365–0.823], $p = 0.004$). Pre-conceptional BMI was associated with emergent CS ($p = 0.001$), vaginal operative delivery ($p = 0.007$) and LGA ($p < 0.001$). A BMI categorized as overweight, obese or severely obese increased the likelihood of emergent CS (OR 1.451 [1.011–2.083], 1.585 [1.070–2.349] and 2.019 [1.385–2.941], respectively) and delivering an LGA fetus (OR 2.020 [1.145–3.565], 2.112 [1.172–3.805] and 3.639 [2.110–6.276], respectively). Underweight mothers (OR 2.911 [1.148–7.382]) were at significantly higher risk of delivering via vaginal operative delivery. Severely obese women (OR 0.425 [0.217–0.832]) on the other hand were at lower risk compared to normal weight women. Maternal age was associated with primary (OR 1.042 [1.019–1.067], $p < 0.001$ for the increase of 1 year) as well as emergent CS (OR 1.031 [1.007–1.055], $p = 0.010$ for the increase of 1 year).

4. Discussion

Our analysis was able to corroborate the existence of three different types of metabolic phenotypes in women with GDM based on the 75 g oGTT levels. Each group revealed specific associations regarding the baseline characteristics as well as fetomaternal outcomes (Figure 4).

	GDM-PH	GDM-IPH	GDM-OH
Mean 75g oGTT glucose levels in mg/dl [a]	**99.02** (±8.35)/ 145.63 (±22.63)/ 116.16 (±19.93)	83.77 (±5.97)/**188.11** (±22.31)/147.28 (±31.28)	**105.84** (±14.95)/ **204.98** (±32.01)/ **158.80** (±36.67)
Nullipara [b]	33.8%	**39.7%**	25.0%
Mean BMI [c]	**28.63** (±6.46)	26.10 (±5.33)	**29.69** (±6.33)
Mean weight gain in kg	12.17 (±7.85)	11.24 (±6.23)	**10.90** (±6.43) [c]
Insulin therapy [c]	**17.54%**	8.85%	**34.26%**
Vaginal delivery [c]	50.5%	**47.8%**	51.3%
Vacuum extraction [c]	8.1%	**9.8%**	5.5%
Primary CS [b]	**24.8%**	18.2%	21.5%
Emergent CS [c]	16.6%	**23.9%**	21.7%
Mean birth weight percentile	**54.68** (±30.16) [b]	49.43 (±29.52)	**57.51** (±29.65) [b]
LGA rate [c]	**12.8%**	6.5%	**18.5%**

[a] Values in this row differ significantly with a p-value < 0.05.
[b] Mean value differs significantly from GDM-IPH with a p-value < 0.05.
[c] Mean value differs significantly from GDM-IPH with a p-value < 0.05.

Figure 4. An overview of significant differences between women of the three subtypes regarding parity, BMI and weight gain, insulin therapy, mode of delivery and fetal growth.

GDM-IFH women were the youngest but had the highest mean weight gain. GDM-CH women were the oldest and displayed the highest number of previous deliveries. Both groups presented with significantly higher pre-conceptional BMI than the GDM-IPH group.

GDM-IFH and GDM-CH women displayed an overall higher rate of well-established GDM risk factors, such as higher maternal age [17] or BMI [18]. This may explain, why GDM-IFH and GDM-CH women received the 75 g oGTT more frequently before 24 GW. The rate of a previous GDM was not assessable through our dataset, although it is an important contributing factor for the development of GDM and should be investigated in further studies [19].

Our results revealed a strong association of GDM-IFH and GDM-CH with the requirement of insulin therapy, which is corroborated by recent studies [14,20–23]. Kotzaeridi et al. affirmed a "worse metabolic profile", higher BMI and an increased requirement for glucose-lowering medications in women with elevated fasting glucose, especially GDM-CH women [15]. Their study additionally revealed a significantly higher BMI in GDM-IFH and GDM-CH patients compared to women without glucose intolerance.

It is well-established that GDM in itself increases the risk of neonates being LGA [4]. We found that GDM-IFH and GDM-CH mothers delivered offspring with significantly higher birth weight as well as birth weight percentiles and increased odds of being LGA at the time of delivery compared to the GDM-IPH group. This aligns with findings of numerous studies, which previously demonstrated that maternal fasting glucose is strongly associated with LGA and higher birth weight [5,12,13]. An analysis by Black et al. revealed higher rates of LGA and increased birth weight in women with fasting hyperglycemia, not only compared to patients with post-load hyperglycemia but to non-GDM patients as well [13]. Uvena-Celebrezze et al. were able to establish a correlation of maternal fasting glucose and neonatal fat mass in a study that used the self-monitoring of glucose levels [24]. Zawiejska et al. showed that maternal fasting hyperglycemia was associated with birthweight $\geq$ 4000 g [14].

The higher rate of LGA in GDM-IFH and GDM-CH groups possibly contributes to an increased rate of primary CS in these groups. The rates of primary CS were highest in the GDM-IFH group, however in the binomial logistic regression only the association of GDM-IFH with primary CS in comparison to GDM-CH reached statistical significance.

The risk of emergent CS was significantly increased in the GDM-IPH and GDM-CH groups compared to GDM-IFH, whereas we found no significant difference among the subgroups regarding cesarean section in general.

GDM-IPH women presented with a lower pre-conceptional BMI, were more likely nulliparous and required insulin therapy less often.

While we found a higher rate of vaginal operative deliveries in women with GDM-IPH, there was no association of the subtypes and vaginal operative deliveries in the logistic regression analysis. However, the odds of a vaginal operative delivery were significantly increased if women were underweight and/or nulliparous. These characteristics were more frequently displayed in the GDM-IPH group; therefore, this could explain the higher rate of vaginal operative delivery. This goes along with a recent analysis, that was able to demonstrate an association of vacuum extraction and nulliparity [25]. Ramos et al. examined women requiring operative delivery assistance and found a decreased likelihood of vaginal operative delivery in women with pre-pregnancy obesity [26].

The rate of SGA was significantly higher in women of the GDM-IPH group; however, SGA did not reach statistical significance in the logistic regression. This may be explained by the strong association between nulliparity and SGA we found in our analysis, as well as the significantly higher rate of nulliparous women in the GDM-IPH group.

Previous studies found correlations of post-load hyperglycemia and gestational hypertension, hyperbilirubinemia and preterm delivery, whereas preterm delivery did not differ significantly among our subgroups and gestational hypertension and hyperbilirubinemia were not evaluated in this study [12–14].

Of note, IUFD and shoulder dystocia did not reach statistical significance, but all reported cases in our sample occurred either in women of the GDM-IFH or GDM-CH subgroups. Several other studies have previously shown associations of maternal fasting glucose and LGA or macrosomia with shoulder dystocia [27]. They found fetal macrosomia to be a mediating factor between maternal fasting hyperglycemia and shoulder dystocia. A meta-analysis by Farrar et al. showed associations of fasting as well as post-load glucose levels with shoulder dystocia, although an increase in fasting glucose was more strongly associated [5].

A limitation of this study was the lack of healthy controls, as we collected the data solely from the gestational diabetes consultation without a control group. The inclusion of normal glucose tolerant women in previous studies, such as Kotzaeridi et al., has provided further insight and the advantage of contextualizing different pathological glucose response patterns [15]. The study population consists of patients exclusively from one GDM consultation clinic in Berlin, Germany, which may have an impact on the generalizability of the results. Additionally, the sample sizes for the individual analyses of variables were not the same throughout the study, due to sporadically missing data. On the other hand, an important advantage is the large sample size and amount of different baseline and outcome parameters that were assessed in this study.

5. Conclusions

To conclude, we did observe significant differences between the GDM subtypes regarding their underlying characteristics and the course of their diagnostic process and were able to identify subtypes that were at higher risk of certain adverse perinatal outcomes. Women categorized as GDM-IFH or GDM-CH were more likely to need a type of insulin therapy, displayed a higher BMI, and their offspring had higher birthweight, birth weight percentiles and were more likely a LGA fetus, while neonates of women with GDM-IPH were at increased risk of low fetal weight. GDM-IFH was associated with primary CS, while GDM-IPH and GDM-CH were associated with emergent CS.

This analysis suggests that the categorization based on the 75 g oGTT glucose levels could be a practicable approach to adapt the prenatal care of women with GDM based on their risk factors. In the future, prospective studies taking the maternal risk factors into account should be conducted, possibly including interventions for women at risk.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

GDM	gestational diabetes mellitus
oGTT	oral glucose tolerance test
oGCT	oral glucose challenge test
CS	cesarean section
GDM-IFH	gestational diabetes with isolated fasting hyperglycemia
GDM-IPH	gestational diabetes with isolated postprandial hyperglycemia
GDM-CH	gestational diabetes with combined hyperglycemia
LGA	large for gestational age
IUGR	intrauterine growth retardation
SGA	small for gestational age
GW	gestational week
IUFD	intrauterine fetal death

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2.4. Spectrum of congenital anomalies of the kidney and urinary tract (CAKUT) including renal parenchymal malformations during fetal life and the implementation of prenatal exome sequencing (WES)

Eine aktuelle Untersuchung bezieht sich auf die Frage, welche Zusatzinformationen durch die Trioexom-Analyse bei fetalen Nierenfehlbildungen (Congenital Malformations of the Kidney and Urinary Tract = CAKUT) gewonnen werden können. Mit einer Prävalenz von 4 bis 60 von 10 000 Lebendgeburten sind pränatal diagnostizierte renale Malformationen häufig diagnostizierte Fehlbildungen (93)**.** CAKUT machen 40 bis 50 % aller schweren kindlichen Niereninsuffizienzen aus und gehören dadurch zu den relevanten pränatal diagnostizierten Malformationen, die einen Einfluss auf die kindliche Gesundheit haben (94)**.** CAKUT kann genetische Ursachen haben, zum Beispiel Aneuploidien, monogene Erkrankungen (wie polyzystische Nierenerkrankung) und Ziliopathien. CAKUT sind in einigen Fällen mit extra-renalen Fehlbildungen assoziiert, vor allem im Rahmen von syndromalen Erkrankungen (95)**.** Die Frage ist also, wie häufig genetische Veränderungen bei fetalen Nierenfehlbildungen zu finden sind und wie die Eltern für die weitere Schwangerschaft betreut werden können.

In dieser Arbeit wurden CAKUT-Fälle aus der Trioexom-Datenbank des Zentrums für genetische Diagnostik, Tübingen herausgesucht und analysiert. Die renalen Fehlbildungen wurden pränatal diagnostiziert. Es erfolgte anschließend eine invasive Diagnostik zunächst mit Bestimmung des fetalen Karyotyps. Wenn dieser unauffällig war, wurde in diesen Fällen die Trioexom-Analyse durchgeführt.

Im Zeitraum August 2018 bis Dezember 2022 konnten aus den 1123 Trioexom-Analysen insgesamt 63 CAKUT-Fälle identifiziert werden (5,6 %). In der deskriptiven Analyse zeigte sich eine Detektionsrate von auffälligen Trioexom-Analysen in 15 von 63 Fällen (23,8 %). In Feten, die isoliert mit einer renalen Malformation auffielen, ergab sich in 11,4 % der Fälle eine pathogene Variante im Trioexom. Dies steht im Gegensatz zu Feten mit assoziierten extra-renalen Fehlbildungen, bei denen in 52,6 % der Fälle ein auffälliger Befund im Trioexom detektiert werden konnte.

Diese Analyse zeigt, dass vor allem bei Feten mit extra-renalen Malformationen eine Trioexom-Analyse im Falle eines unauffälligen Karyotyps relevante Zusatzinformationen liefern kann.

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MATERNAL-FETAL MEDICINE

Spectrum of congenital anomalies of the kidney and urinary tract (CAKUT) including renal parenchymal malformations during fetal life and the implementation of prenatal exome sequencing (WES)

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Abstract

Objectives and background Congenital malformations of the kidney and urinary tract (CAKUT) have a prevalence of 4–60 in 10,000 livebirths and constitute for 40–50% of all end stage pediatric kidney disease. CAKUT can have a genetic background due to monogenetic inherited disease, such as PKD or ciliopathies. They can also be found in combination with extra-renal findings as part of a syndrome. Upon detection of genitourinary malformations during the fetal anomaly scan the question arises if further genetic testing is required. The purpose of this study was to determine the phenotypic presentation of CAKUT cases and the results of exome analysis (WES).

Methods This is a retrospective analysis of 63 fetal cases with a diagnosis of CAKUT or DSD at a single center between August 2018 and December 2022.

Results A total of 63 cases (5.6%) out of 1123 matched CAKUT phenotypes including renal parenchyma malformations. In 15 out of 63 WES analysis a pathogenic variant was detected (23.8%). In fetuses with isolated CAKUT the rate of detecting a pathogenic variant on exome sequencing was five out of 44 (11.4%). Ten out of 19 fetuses (52.6%) that displayed extra-renal findings in combination with CAKUT were diagnosed with a pathogenic variant.

Conclusions WES provides an increase in diagnosing pathogenic variants in cases of prenatally detected CAKUT. Especially in fetuses with extra-renal malformations, WES facilitates a gain in information on the fetal genotype to enhance prenatal counselling and management.

Keywords CAKUT · PKD · DSD · Exome sequencing · WES · Detection rate · Polycystic kidney disease · Ectopic kidney · Horseshoe kidney · Urinary tract dilation

Abbreviations

CAKUT	Congenital malformations of the kidney and urinary tract
PKD	Polycystic kidney disease
DSD	Disorders of sex development
NIPT	Non-invasive prenatal testing
CAH	Congenital adrenal hyperplasia
WES	(Whole) exome sequencing
LUTO	Lower urinary tract obstruction
VUS	Variant of unknown/uncertain significance
DNA	Deoxyribonucleic acid
CMA	Chromosomal microarray analysis
MCKD	Multicystic kidney disease

What does this study add to the clinical work

This study analyses cases of CAKUT and the rate of pathogenic variant in exome sequencing (WES). The results indicate that especially among fetuses with polycystic kidney disease or associated extra-renal malformations the rate of pathogenic finding is highest (29% and 52.6% respectively).

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Introduction

Fetal abnormalities can be detected prenatally in around 2–3% of pregnancies [1, 2]. Upon detection, parental genetic counselling is offered together with invasive diagnostic procedures such as amniocentesis and chorionic villous sampling performing a karyotype and/or chromosomal microarray analysis (CMA). Overall, 8–10% of fetuses with an anomaly display an abnormal karyotype with an additional 6% of microdeletions and microduplications, which leaves most fetuses without a specific genetic diagnosis [3]. Depending on the publication, exome sequencing can detect a pathogenic variant in 20–80% of cases, if the karyotype or CMA is negative [4–7]. Prenatal WES can expand the yield of diagnosing an underlying disease in prenatally detected fetal abnormalities and it has the potential to increase the knowledge on prenatal disease [8].

Congenital anomalies of the kidney and urinary tract (CAKUT) including renal parenchymal malformations are detected in 20–30% of all fetal anomalies, identified during the prenatal scan [9]. The second trimester anomaly scan has become a standard of care provided for almost all risk pregnancies in Germany [10]. Some urinary tract malformations are detected during the third trimester scan, as a form of late onset CAKUT.

CAKUT is a heterogeneous group of fetal malformations that affect the development of the kidneys and their outflow tracts (Fig. 1) [11, 12]. The prevalence is estimated to be around 4–60 in 10,000 births [13]. Extra-renal anomalies are detected in 30% of infants with CAKUT [9].

The development of the urinary tract is a multistage process, that is initiated by the ureteric bud and the metanephron at five gestational weeks. Any disturbance at any stage of the renal development can lead to different types of CAKUT with more severe defects occurring based on disruptions during early embryonic development [14–16]. The abnormal embryonic kidney development can be caused by renal parenchymal malformations (e.g., congenital cystic kidney disease), abnormal renal migration (e.g., altered position of the renal tissue) and disturbance in the developing renal collecting system (e.g., urinary tract obstruction) [17, 18]. CAKUT can be divided into non-genetic and genetic origins [19]. Certain teratogens, including drugs are known to cause an impairment of kidney development (e.g., ACE inhibitors and warfarin) [20]. The spectrum of CAKUT can range from almost no impairment to end stage renal disease requiring kidney transplantation or to a lethal condition due to pulmonary hypoplasia [15, 21]. Therefore, early detection during the prenatal ultrasound is essential to facilitate parental counselling and a close fetal and neonatal follow-up. Today, children affected by CAKUT have better chances of survival due to an improvement in early diagnosis, interventions and dialysis as well as kidney transplantation. Depending on the type of CAKUT severe comorbidities can be associated, impacting on overall survival and quality of life [19].

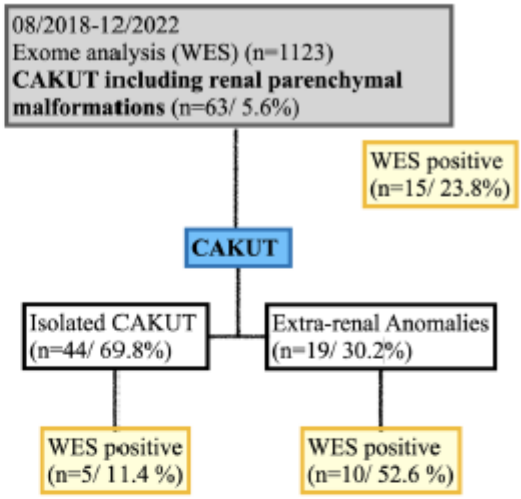

Fig. 1 Description of the study population grouped according to the fetal phenotype. A total of 63 cases were analyzed during the investigation period (08/2018–12/2022)

This study focuses on the additional information in diagnosing pathogenic variants, when performing WES after a negative karyotype and/or microarray upon detection of CAKUT prenatally.

Materials and methodology

We searched the whole exome sequencing data bank at the Center of Human Genetics in Tübingen, Germany for cases of prenatally detected CAKUT including renal parenchymal malformations. A total number of 1123 WES were conducted from August 2018 until December 2022. Patient information was systematically reviewed including demographic factors, prior analysis and outcome. The genetic analysis was performed due to either CAKUT alone or combined with extra-renal findings concerning the fetal phenotype. As keywords we searched: CAKUT, polycystic kidney disease, hydronephrosis, megaureter, megacystis, LUTO, ureterocele, horseshoe kidney, ectopic kidney, fused kidney, kidney duplication, enlarged kidney, small kidney, hyperechogenic kidney. 63 cases out of 1123 (5.6%) matched the keywords. Descriptive analysis was performed applying SPSS version 22, IBM.

Genetic analysis

Trio exome sequencing of our own cohort DNA quantity and quality were determined using Qubit Fluorometer and NanoDrop ND-8000 (Thermo Fisher Scientific, Dreieich, Germany). Enrichment of the coding DNA sections of the test persons was carried out with one of the following enrichment methods: SureSelect Human All Exon 50 Mb V6 Kit, SureSelect Human All Exon 50 Mb V7 Kit (Agilent, Santa Clara, CA, USA), the Twist Human Core + Refseq exome (Twist Bioscience, San Fransisco, CA, USA) or the CeGaT Exome Xtra V1 (CeGaT GmbH, Tübingen, Germany). For Agilent enrichment kits, sequencing libraries were prepared using the SureSelectXT workflow. Library preparation and capture for all samples was performed according to the respective manufacturer's instructions. Paired-end sequencing was performed using the Novaseq6000 system (Illumina, San Diego, CA) with 2 × 100 base pairs (bp) read length. Sequence data were processed with Illumina bcl2fastq2. Adapter sequences were removed with Skewer and the sequences obtained were aligned to the human reference genome (hg19) with the Burrows Wheeler aligner (BWA mem). Sequences that could not be clearly assigned to a genomic position were removed, as were sequence duplicates that were probably due to amplification (internal software). The average coverage was 170x. Sequence variants (single nucleotide exchanges and short insertions/deletions) were determined from the remaining high-quality sequences (CeGaT StrataCall). Copy number variations (CNV) were computed on uniquely mapping, non-duplicate, high quality reads using an internally developed method based on sequencing coverage depth. Briefly, we used reference samples to create a model of the expected coverage that represents wet-lab biases as well as intersample variation. As a prediction software Mutationtaster, SpliceAI and NSFP was utilised parallely.

Results

From August 2018 until December 2022 a total of 63 cases (5.6%) out of 1123 were analysed. The Center for Human Genetics received fetal DNA from all over Germany. The fetuses received a primary diagnostic ultrasound scan at a specialised prenatal diagnosis unit. The prenatal scan was conducted as a systemic evaluation of the fetal anomaly including echocardiography based on international recommendations [22–25]. The mean maternal age was 33.2 years (range 19–41 years, SD ± 5.14). The mean gestational week at testing was 23.2 (range 14–35, SD ± 5.32). In 11 studies (17.4%) exact data on GW was missing. 3.2% (2) of DNA samples were obtained postmortem. 7.9% (5) of fetuses were diagnosed during the first trimester, 52.4% (33) during the second trimester and 19.1% (12) in the third trimester. In 96.9% (61) the DNA sample was derived from a prenatal sample [amniocentesis in 58 cases (92.1%), chorionic villous sampling in three cases (4.8%)] and postmortem DNA sampling in two cases (3.1%). No confined placental mosaicisms (CPM) was detected among our cohort. The initial genetic test that was requested upon detection of a fetal malformation was a karyotype in 69.8% and a chromosomal microarray analysis in 28.6% (in one case the initial genetic test was not specified) (Table 1). In our cohort, the initial genetic test did not reveal a pathological finding, and therefore, further analysis was performed. Incidental findings were reported in five out of the 63 cases (7.9%). A variant of unknown/uncertain significance (VUS) was detected in two fetuses (3.2%). A trio exome sequencing (trio WES) was conducted in 61 cases (96.8%). In two fetuses a single WES was performed. The mean turnaround time was 13.3 days (median 12 days, range 6–42 days, SD ± 6.02). Sanger validation of variants was performed in 98.4%.

Detection rate

In 15 out of 63 WES analysis a pathogenic variant was detected (23.8%) (Fig. 1, Table 2, figure). In fetuses with isolated CAKUT the rate of detecting a pathogenic variant by exome sequencing was five out of 44 (11.4%). Ten out of 19 fetuses (52.6%) that displayed extra-renal findings in combination with CAKUT were diagnosed with a pathogenic variant. The associated findings were of the fetal face (cleft palate), the central nervous system (vermian hypoplasia, dilated cisterna magna), of the neck (lateral cervical cysts), thorax (diaphragmatic hernia, pulmonary hypoplasia), heart (not specified), abdomen (omphalocele, gastroschisis, microcolon), extremities (club feet, arthrogryposis), fetal hydrops and genital malformation (hydrometrocolpos, cloacal malformation). In addition, there were associated abnormal findings of the fetal growth (IUGR, macrosomia) and the amniotic fluid (polyhydramnios, oligohydramnios, anhydramnios). Three pregnancies underwent termination, among these was a case of bilateral renal agenesis, and two fetuses with LUTO.

In fetuses with isolated renal anomalies, the highest detection rate of pathogenic variants was among fetuses with isolated polycystic kidney disease (29% PKHD1, PKHD1, PKD1, ETFA). One fetus out of four with bilateral renal agenesis was diagnosed with HNF1B (25%). All other isolated CAKUT cases did not reveal a pathogenic variant in WES (Table 2).

A higher detected rate was found in fetuses with CAKUT and extra-renal findings: 10 out of 19 fetuses (52.6%) were diagnosed with a pathogenic variant. Three of six fetuses with polycystic kidney disease and extra-renal abnormalities displayed a pathogenic variant (INVS, TP63, CEP290).

Table 1 Baseline data on genetic testing in numbers and percentage or mean and median

	n	Percentage	Mean; median (range)
Initial genetic testing			
Karyotype	44	69.8%	
Chromosomal microarray analysis	18	28.6%	
Not specified	1	1.6%	
Incidental findings			
None	58	92.1%	
Reported	5	7.9%	
Variant of unknown significance detected			
None	61	96.8%	
Reported	2	3.2%	
Type of exam			
Single	2	3.2%	
Duo	0	0.0%	
Trio	61	96.8%	
Type of NGS			
Clinical ES	0	0.0%	
WES	63	100.0%	
WGS	0	0.0%	
Turnaround time NGS (in days)			13.3; 12 (6–42)

NGS next generation sequencing, *WGS* whole genome sequencing

Table 2 Specific detection rate of pathogenic variants for each fetal phenotype ± associated malformations divided into two groups: isolated CAKUT and non-isolated CAKUT

CAKUT	Isolated CAKUT			Non-isolated CAKUT		
	Total	Proportion with abnormal genetic testing (%)	Pathogenic variant	Total	Proportion with abnormal genetic testing (%)	Pathogenic variant
Renal agenesis (*n* = 14)						
Renal agenesis bilateral (*n* = 7)	4	1 (25%)	*HNF1B, TBC1D1*	3	0	
Renal agenesis unilateral (*n* = 7)	6	0		1	1 (100%)	*Hypomethylation C2*
Renal hypoplasia (*n* = 5)	3	0		2	2 (100%)	*GREB1L*
						POGZ
PKD (*n* = 20)	14	4 (29%)	*PKHD1*	6	3 (50%)	*INVS*
			PKHD1			*TP63*
			PKD1			*CEP290*
			ETFA			
Renal hyperplasia (*n* = 3)	3	0		0	0	
Hyperechogenic kidneys (*n* = 1)	1	0		0	0	
Horseshoe kidneys (*n* = 7)	5	0		2	1 (50%)	*KMT2A*
Hydronephrosis (*n* = 7)	4	0		3	2 (67%)	*FREM1*
						KANSL1
LUTO (*n* = 6)	4	0		2	1 (50%)	*CHD7*
	44	5 (11.4%)		19	10 (52.6%)	

Some of the CAKUT cases with associated malformations did reveal a pathogenic variant in WES (unilateral renal agenesis Hypomethylation C2; horseshoe kidney KMT2A; hydronephrosis FREM2, KANSL1; LUTO CHD7; renal hypoplasia GREBIL, POGZ).

Specific genetic findings (additional material)

The definitive genetic variants detected in the affected fetuses are listed in Table 3. Polycystic kidney disease (PKD) is the most common inherited kidney disease [26, 27]. There

are two types: the frequently encountered autosomal dominant polycystic kidney disease (ADPKD) and more rare autosomal recessive polycystic kidney disease (ARPKD) as the most common types of monogenic cystic kidney disease. ADPKD often becomes apparent as adults, whereas ARPKD appears at a very young age or even during pregnancy as it is accompanied by an early and severe impairment of kidney function. Both types can lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD). ADPKD is the most frequent PKD with a prevalence of 1:400–1000 deliveries [27]. Extra-renal anomalies are described and manifest in the liver, the blood vessels and the heart. Mortality is most often caused by cardiac complications or infectious diseases during renal replacement therapy. ADPKD is associated with autosomal dominant PKD1 or PKD2 loss [27, 28]. PKD2 loss is described to have a milder phenotype than PKD1 loss associated with a lower incidence of ESRD [26]. Prenatally ADPKD is associated with enlarged bilateral kidneys with or with hyperechogenicity [29]. As a differential diagnosis ADPKD, congenital nephrosis of the finnish type, Meckel Gruber syndrome, Trisomy 13 and Beckwith Wiedemann, as well as loss of HNF1B can appear prenatally with a similar phenotype with enlarged hyperechogenic kidneys [30].

In our cohort, one case of Glutaric acidemia type II was detected (EFTA variant). It is an autosomal recessive syndrome caused by defects in electron transport flavoprotein (ETF) or ETF–ubiquinone oxidoreductase (ETF–QO) causing hypo- or nonketotic hypoglycemia and metabolic acidosis. Glutaric acidemia type II can be subdivided into 3 subtypes with different ages of onset, whereas early onset (in neonatal period) comes with the highest mortality. Patients have kidney abnormalities, hypotonia, cardiomyopathies as well as liver abnormalities, weakness, fatigue and myalgia [31]. The prevalence is 1:250,000 [32].

One fetus from our cohort was diagnosed with TP63-related disorder. TP63-related disorders are a spectrum of six autosomal dominant syndromes including Ankyloblepharon–ectodermal defects–cleft lip/palate (AEC) syndrome; Acro-dermo-ungual–lacrimal–tooth (ADULT) syndrome; Ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (EEC3); Limb–mammary syndrome; Split-hand/foot malformation type 4 (SHFM4) and Isolated cleft lip/cleft palate (orofacial cleft 8) [33–35]. Depending on the disorder affected individuals can display different combinations of ectodermal dysplasia (hypohidrosis, nail dysplasia, sparse hair, tooth abnormalities), cleft lip/palate, split-hand/foot malformation, syndactyly, oligodactyly and other limb anomalies, lacrimal duct obstruction, hypo- or hyperpigmentation, hypoplastic breasts and/or nipples, hypospadias, abnormalities of kidneys and urinary tract. Furthermore, affected individuals can show attached eyelids, skin erosions and erythema, scarring of the scalp, alopecia, trismus, multiplenfreckles and specific facial characteristics (hypoplasia of the maxilla, wide nasal root, small alae nasi and a small red of the upper lip). Most patients suffer from impaired hearing (AEC syndrome). The prevalence of T63-related disorders is not yet fully investigated [35].

Nephronophthisis (NPH) describes a heterogenous group of autosomal recessive inherited kidney disease that is associated with multiple cysts causing fibrosis, inflammation and conclusively ESRD. NPH belongs to the group of ciliopathies, and it can be categorized infantile, juvenile and adolescent depending on the age of onset. Juvenile NPH has an incidence of 1:50,000 to 1:1,000 000 [36]. The loss of the NPHP1 gene and more than 20 other genes causes NPH (Wolf). Extra-renal anomalies associated with NPH can be cerebellar malformations, ocular anomalies, hepatic fibrosis and skeletal malformations depending on the underlying genetic cause. In our cohort, INVS loss was detected, which caused nephronophthisis. NPH-associated syndromes are Meckel–Gruber syndrome, Bardel–Biedl syndrome, Joubert syndrome as well as Jeune syndrome and other rarer conditions [37–40].

In our cohort, there was one case of Joubert syndrome 5 (variant of CEP290). Classic Joubert syndrome (JS) is an autosomal recessive disease describing a combination of molar tooth sign (MTS, abnormality of cerebellum and brain stem), hypotonia and retardation of development [40, 41]. Furthermore, affected individuals possibly suffer from respiratory issues, such as tachypnea or apnea, eye abnormalities, ataxia and mental retardation. The prevalence of the Joubert syndrome and related disorders is 1:80,000–100,000. The prognosis of the syndrome mainly depends on the degree of respiratory disorders but also on the graduation of functional loss of kidneys and liver especially after apneas usually decrease within the first year of life [42].

One fetus was diagnosed with BNAR syndrome through an FREM1 variant. BNAR syndrome describes a rare autosomal recessive disorder characterized by hypertelorism, a bifid or broad nasal tip, short and bulky oral frenula with or without the presence of anorectal defects (anal stenosis, ventrally shifted anus) and renal dysplasia/agenesis without intellectual disability. This bifid nose was not detected in the fetus prenatally. In addition, there can be airway abnormalities. The prevalence is not known yet [43, 44].

Koolen-de Vries syndrome was detected in one fetus (KANSL1 variant). It is an autosomal dominant disorder affecting female and male individuals in the same way and frequency. The affected individuals show a combination of growth restriction, developmental delay (psychomotor, language development), intellectual disability, muscular hypotonia, feeding difficulties, typical facial characteristics and epilepsy. Furthermore, congenital malformations are described affecting the heart and the urogenital system. Life expectancy is not yet clearly defined; however, affected individuals usually reach adulthood. The prevalence

Table 3 Specific gene variants detected on WES, with inheritance and classification of the variant

Syndromes	Affected gene	Classification of the variant	Inheritance/de novo	Type of NGS	Initial genetic testing	CAKUT ultrasound finding	Other malformations
Polycystic kidney disease 1	PKD1: c.8333dupG; p.Glu2779Argfs*43	Significant	Paternal inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	None
Polycystic kidney disease 4	PKHD1: c.1486C>T; p.Arg496*; c.8206T>G; p.Trp2736Gly	Significant	Paternal and maternal inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	None
Polycystic kidney disease 4	PKHD1: c.11438delT; p.Phe3812Serfs*7	Significant	Maternal inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	None
Glutaric Acidemia IIA	ETFA: c.15_25dup; p.Gln9Argfs*20	Significant	Paternal and maternal inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	None
Spectrum of TP63-related disorders	TP63: c.1717_1719dupATC; p.Ile573dup	Significant	De Novo	WES (trio)	Karyotype	Megaureter hydronephrosis unilateral polycystic kidneys	Cleft palate
Infantile Nephronophthis	INVS: c.1417delG; p.Ala473GlnfsX37	Significant	Paternal And Maternal Inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	Situs Inversus
Joubert Syndrome 5	CEP 290: c.5813_5817delCTTTA; p.Thr1938Asnfs*16 hom	Significant	Paternal And Maternal Inheritance	WES (trio)	Karyotype	Bilateral polycystic kidneys	Vermian hypoplasia dilated cisterna magna
BNAR Syndrome	FREM1: c.2078+1G>T; p.?, c.3274+4A>G; p.?	Significant	Paternal And Maternal Inheritance	WES (trio)	Karyotype	Urogenital sinus hydronephrosis unilateral renal agenesis	Hydrometrocolpos cloacal malformation
Koolen-De Vries Syndrome	KANSL1: c.1534-1G>C; p.?	Significant	De Novo	WES (trio)	Karyotype	Hydronephrosis	Hydrops lateral cervical cysts
CHARGE Syndrome	CHD7: c.5405-7G>A; p.?	Significant	De Novo	WES (trio)	Karyotype	Megacystis	Multiple Malformations (Not Specified)
Renal Cysts and Diabetes Syndrome (HNF1B), congenital Anomaly of the Kidneys and the Genitourinary Tract (TBC1D1)	HNF1B; c.1006C>G; p.His336Asp, TBC ID 1: c.1326G>C; p.Gln442His	Variant of unknown significance	Unknown	WES (single)	Karyotype	Bilateral Renal Agenesis	None
White-Sutton Syndrome	POGZ: c.2513_2514insT; p.Ser839Leufs*25	Significant	De Novo	WES (trio)	Karyotype	Bilateral kidney hypoplasia	Club feet
Renal hypoplasia 3	GREB1L: c.1735C>T; p.Arg579*	Significant	Maternal Inheritance	WES (trio)	Karyotype	Bilateral kidney aplasia	Cardiac anomaly (not specified)

Table 3 (continued)

Syndromes	Affected gene	Classification of the variant	Inheritance/de novo	Type of NGS	Initial genetic testing	CAKUT ultrasound finding	Other malformations
Beckwith-Wiedemann Syndrome	Hypomethylation IC2	Significant	De Novo	WES (trio) and Multiplex ligation-dependent probe amplification (MLPA)	Karyotype	Unilateral kidney agenesis	Facial anomaly (not specified) omphalocele
Wiedemann-Steiner Syndrome	KMT2A, C.7874G>T; p.Arg2625Leu	Significant	De novo	WES (trio)	Karyotype	Horseshoe kidneys	Cardiac and pulmonary anomalies (not specified)
Prenatally diagnosed findings of CAKUT and extra-renal findings							

of Koolen-de Vries syndrome is not fully investigated yet [45–47].

One fetus with multiple anomalies was diagnosed with CHARGE syndrome prenatally (CHD7 variant). It is a multisystemic disorder. CHARGE is an abbreviation, standing for: coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities including deafness. CHARGE syndrome is detected in 1/10,000 newborn children with a heterogenous phenotype associated with a potentially poor outcome [48, 49].

Renal cysts and diabetes syndrome (RCAD) is caused by HNF-1ß-mutations. Inheritance is autosomal dominant, and the prevalence of the syndrome is not known. Kidneys show diverse sizes, most patients show enlarged kidneys prenatally and as a child, whereas affected adults often show a scaling down of the kidneys. The syndrome often leads to renal replacement therapy including kidney transplantation [50]. The onset and diagnosis of diabetes varies between 10 and 61 years. Extra-renal manifestations can be genital tract malformations, hyperuricaemia, gout as well as pathological liver function [51–53].

White–Sutton syndrome is an autosomal dominant disease caused by a POGZ variant encompassing a combination of intellectual disability, developmental retardation, facial dysmorphism, hypotonia, autism spectrum disorder and behavioral abnormalities [54, 55]. The facial appearance of the affected individuals is characterized by micro-/brachycephaly, a prominent forehead, hypertelorism, prognathism, downward facing corners of the mouth, expanded nasal bridge with frontally facing nostrils, low-set ears and palate abnormalities [56]. Affected individuals have been reported to reach more than 30 years of age and to have children.

Renal hypoplasia can be subdivided into four subtypes: segmental hypoplasia, Oligomeganephronia, simple hypoplasia and cortical hypoplasia. The inheritance follows autosomal dominant patterns. All types are considered to have less renal lobes compared to normal kidneys, different phenotypes of the kidneys. All types of renal hypoplasia may remain unknown for a long time, developing increasing loss of renal function [57]. All types are considered to have less nephrons compared to a normal kidney. In the majority of cases a normal contralateral kidney can be seen. The healthy kidney might compensate for the loss of function and grow larger than usual. All types of renal hypoplasia may remain unknown for a long time, developing increasing loss of renal function [57].

Beckwith–Wiedemann syndrome is a genomic imprinting disorder causing overgrowth and a predisposition to embryonal tumors, mostly Wilms tumor and hepatoblastoma [58–60]. The clinical phenotype is variable, often showing macroglossia and possible abdominal wall defects

and abnormalities of liver, spleen, pancreas, kidneys and adrenals. The prevalence is 1:26,000 deliveries [61].

Wiedemann–Steiner syndrome (WSS) is detected in less than 1 out of 1,000,000 individuals [62]. The inheritance is autosomal dominant, and the age of onset can be between the prenatal period and childhood. The syndrome mainly describes the combination of growth restriction, developmental and cognitive retardation combined with a characteristic facial appearance. Apart from that, patients can be affected by epilepsy, ophthalmologic anomalies, congenital heart defects, hypotonia, vertebral anomalies, renal and uterine anomalies, dysfunction of the immune system, brain malformations and dental abnormalities. Developmental and cognitive delay shows very variable graduations. Overall, the effect on daily life of WSS on affected individuals varies from hardly noticeable symptoms to severe disabilities.

Discussion

This study focuses on the detection rate of pathogenic variants in WES in fetuses with CAKUT including renal parenchymal malformations. The rate of prenatal CAKUT was relatively low with 5.6% among all performed WES at the data bank at the Center of Human Genetics in Tübingen, Germany. The overall detection rate of a pathogenic variant in our cohort was 23.8%. The highest yield of detection was among fetuses with extra-renal findings with 52.6% vs. 11.4% in fetuses with isolated CAKUT. A variety of pathogenic variants were detected with differing neonatal prognosis in our cohort (Table 2).

In literature, WES can detect a pathogenic variant in 20–80% of cases when the karyotype or CMA is negative [4–7]. The diagnostic yield of WES in prenatal CAKUT has been described between 0% and 16% [63, 64]. Another publication supports our finding, that fetuses with extra renal anomalies display a higher diagnostic rate of pathogenic variants than fetuses with isolated renal findings (25% vs. 9.1%, respectively) [7]. We suggest the following diagnostic chronology (Fig. 2): initially, the sonographer should distinguish between structural/dysplastic kidneys (as in PKD, hyperechogenic kidneys) and outflow obstruction/renal agenesis and ectopic kidneys. Upon detection one should always search for extra-renal abnormalities. Genetic counselling should be offered. In case of simple outflow obstruction/renal agenesis and ectopic kidneys invasive/non-invasive genetic testing can be offered. In the case of extra-renal anomalies invasive genetic testing is advisable. If the karyotype/CMA is negative further testing as in WES should be discussed and offered. A recent study on 46 fetuses with megacystis and subsequent vesico-amniotic shunting (VAS), were able to distinguish between isolated (61%) and complex megacystis (39%) cases [65]. Interestingly, the rate of

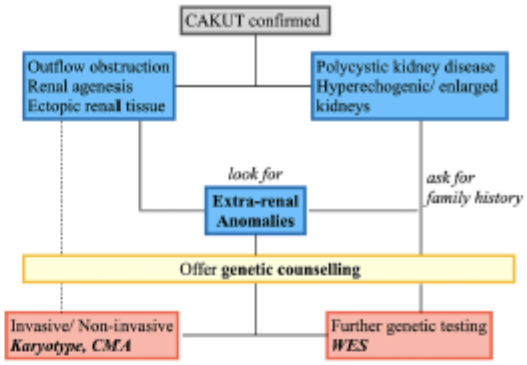

Fig. 2 Counselling suggestion on further genetic testing upon prenatal detection of CAKUT: initially, it should be distinguished between structural/dysplastic kidneys (such as PKD, hyperechogenic kidneys) and outflow obstruction/renal agenesis and ectopic kidneys. Extra-renal abnormalities should be excluded. Genetic counselling should be offered. If simple outflow obstruction/renal agenesis and ectopic kidneys is apparent invasive/non-invasive genetic testing can be offered. In case of extra-renal anomalies invasive genetic testing is advisable. If karyotype/CMA is negative further testing as in WES should be discussed. If polycystic/hyperechogenic kidneys with or without extra-renal anomalies are detected prenatally invasive genetic testing should be discussed. Family history has to be taken into account. If the karyotype/CMA is negative further testing as in WES should be offered if available

neonatal survival was much higher among the isolated mega cystic cohort (96.4% vs. 63.6% in the complex megacystis group). In our cohort, 6 fetuses with LUTO were identified, 2 displayed extra-renal findings out of which one fetus was diagnosed with CHD7 loss. In the future, further analysis should be conducted on genetic findings in fetuses with megacystis, to answer the question if complex megacystis case are associated with a complex genetic mutation. The answer will help facilitate counselling families prior to VAS.

If polycystic/hyperechogenic kidneys with or without extra-renal anomalies are detected prenatally invasive genetic testing is advisable. Family history should always be considered. If the karyotype/CMA is negative further testing-like WES should be offered.

Sequential sonographic follow-up and individualized care is required upon detection of CAKUT. Termination of pregnancy can be discussed and offered based on national legislation in cases with poor prognosis (e.g., lung hypoplasia due to renal mal-/dysfunction or specific pathogenic variants associated with unfavorable outcome).

This study has limitations such as missing data on the neonatal outcome and fallow-up. This issue should be addressed in future studies. Furthermore, some CAKUT cases are not highlighted in this study as they were not assessed via exam sequencing. Therefore, the resulting selection reduces the generalisability of this analysis. The

rates of fetal anomalies may be overestimated. Further studies with larger cohorts are required to address this question.

Conclusion

The wide availability of exome sequencing is revolutionizing our understanding of genetic causes of prenatal abnormalities including CAKUT. This analysis is so far the largest study on the implementation of WES in CAKUT. Upon prenatal detection of fetal CAKUT we suggest a thorough ultrasonographic scan to exclude associated extra-renal anomalies (Fig. 2). An individualized approach is necessary based on the sonographic findings (renal findings and extra-renal findings) considering the parental preference on finding out the underlying genotype. All patients should receive genetic counselling with the offer of genetic testing (non-invasive vs. invasive). If the karyotype or CMA is negative further genetic analysis can be offered (including WES). Based on our research, the highest detection yield of relevant pathogenic variants is among fetuses with renal and extra-renal findings (43.5% vs. 12.5% in fetuses with isolated CAKUT).

Authors' contribution KJT data analysis, manuscript writing. FL manuscript editing, figure design. RC table design. WA manuscript editing. HW manuscript editing. BS data collection supervision. GH-P data collection or management.

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Data availability The data supporting the findings of this study are available upon request.

Declarations

Conflict of interest All authors declare to have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Exome sequencing was performed as a clinical service under clinical consent forms. Retrospective collection of data from patient records has been granted a waiver of informed consent, as all clinical data contained in this report have been anonymized.

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2.5. Semi-Automatic Measurement of Fetal Cardiac Axis in Fetuses with Congenital Heart Disease (CHD) with Fetal Intelligent Navigation Echocardiography (FINE)

Angeborene Herzfehler (Congenital Heart Disease = CHD) gehören zu den häufigsten fetalen Fehlbildungen, die im Rahmen der Pränataldiagnostik identifiziert werden können. Eine frühzeitige, genaue Diagnose ermöglicht weiterführende Untersuchungen sowie eine interdisziplinäre Beratung der Schwangeren. Mit diesen Ergebnissen können die werdenden Eltern eine informierte Entscheidung bezüglich der Weiterführung der Schwangerschaft und der Geburtsplanung treffen. Die Geburt an einem spezialisierten Zentrum mit direkter kinderkardiologischer Betreuung wirkt sich positiv auf das neonatale Outcome aus (96, 97).

Fetal Intelligent Navigation Echocardiography (FINE) ist eine computerisierte automatische Anwendung, die neun Standard-Echokardiographie-Ebenen generieren kann (98–103). Damit ist eine umfassende Beurteilung der fetalen Herzanatomie möglich. Zusätzlich kann eine Messung der kardialen Achse erfolgen. Es gibt zahlreiche Hinweise darauf, dass die fetale Herzachse bei CHD vom normalen Range (40–45◦) abweicht (98-100). In dieser Arbeit wurden retrospektiv 545 FINE-Volumina von fetalen CHD und Thoraxanomalien mit 1543 FINE-Volumina von Feten mit einem unauffälligen Phänotyp verglichen. Es erfolgten die Messung der fetalen Herzachse und die Eingruppierung nach CHD/Thoraxanomalie.

Die Ergebnisse der Studie zeigten, dass die fetale Herzachse bei 86 % der Feten mit CHD/Thoraxanomalie vom normalen Range abwich. Es konnten spezifische CHD identifiziert werden, die mit einem signifikanten Abweichen von der normalen Herzachse in Verbindung stehen: hypoplastisches Linksherzsyndrom, Pulmonalatresie, Fallot'sche Tetralogie (*p*Wert < 0,0001), rechtsseitiger Aortenbogen, Situs ambiguus (*p*-Wert = 0,0001 bis 0,001) sowie Absent Pulmonary Valve Syndrome, Double Outlet Right Ventricle und thorakale Tumore (*p*-Wert = 0,001 bis 0,01).

Die Analyse verdeutlicht, wie relevant die fetale Herzachse bei der Diagnose eines CHD oder einer Thoraxanomalie sein kann. Die fetale Herzachse kann bei der Routineuntersuchung in der Pränataldiagnostik erhoben werden. Ein Abweichen von der normalen Herzachse kann ein wegweisender Hinweis auf eine Fehlbildung sein.

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Semi-Automatic Measurement of Fetal Cardiac Axis in Fetuses with Congenital Heart Disease (CHD) with Fetal Intelligent Navigation Echocardiography (FINE)

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Abstract: Congenital heart disease (CHD) is one of the most common organ-specific birth defects and a major cause of infant morbidity and mortality. Despite ultrasound screening guidelines, the detection rate of CHD is limited. Fetal intelligent navigation echocardiography (FINE) has been introduced to extract reference planes and cardiac axis from cardiac spatiotemporal image correlation (STIC) volume datasets. This study analyses the cardiac axis in fetuses affected by CHD/thoracic masses (n = 545) compared to healthy fetuses (n = 1543) generated by FINE. After marking seven anatomical structures, the FINE software generated semi-automatically nine echocardiography standard planes and calculated the cardiac axis. Our study reveals that depending on the type of CHD, the cardiac axis varies. In approximately 86% (471 of 542 volumes) of our pathological cases, an abnormal cardiac axis (normal median = 40–45°) was detectable. Significant differences between the fetal axis of the normal heart versus CHD were detected in HLHS, pulmonary atresia, TOF (p-value < 0.0001), RAA, situs ambiguus (p-value = 0.0001–0.001) and absent pulmonary valve syndrome, DORV, thoracic masses (p-value = 0.001–0.01). This analysis confirms that in fetuses with CHD, the cardiac axis can significantly deviate from the normal range. FINE appears to be a valuable tool to identify cardiac defects.

Keywords: fetal cardiac axis; FINE; fetal intelligent navigation echocardiography; CHD; congenital heart disease; AI

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1. Introduction

Congenital heart disease is the most common organ-specific fetal malformation with an incidence of 8–10 per 1000 (0.8–1%) liveborn [1,2]. Children with CHD are associated with increased short-term and long-term morbidity and mortality [3–6]. About 50–60% of patients with CHD will require cardiac surgery [7]. Early diagnosis of CHD during the prenatal period provides information for the parents to enable counseling and decision-making on the fetal outcome and enables diagnostic tests (e.g., genetic, infectious, metabolic) to rule out an underlying cause for the specific CHD. Interdisciplinary counseling, including neonatologists, pediatric cardiac surgeons, and pediatric cardiologists, as well as psychologists and social workers, can be initiated upon early detection of CHD. Furthermore, the delivery of the fetus affected by CHD can be planned in a perinatal center with a pediatric cardiac surgery unit, which, therefore, improves neonatal survival [8].

The development of echocardiography was initiated in the 1960s. In 1954, Edler and Hertz from the University of Lund, Norway, demonstrated cardiac time-motion or

M-mode recordings via ultrasound [9]. In 1972, Nanda and Gramiak from the University of Rochester were able to depict the pulmonary valve through M-mode, which led to an exponential development of echocardiography and the detection of CHD [10]. In the 1970s, fetal application in echocardiography advanced significantly. Kleinman established M-mode and B-mode examinations of the fetal heart, effectively diagnosing cases with CHD [11]. Over the next decades, fetal echocardiography experienced further advances by applying color Doppler, three- and four-dimensional imaging techniques, as well as computerized imaging [12]. Today, fetal echocardiography is an essential component of the fetal anomaly scan and finds a routine application during the first, second, and third-trimester scans.

The visualization of the four-chamber view (4CV) in fetal echocardiography is crucial for several reasons [13]. Firstly, it allows a comprehensive assessment of the fetal heart's structure and functionality. It provides a clear visualization of the atria, ventricles, AV valves, and the inter-ventricular septum, thus enabling the detection of up to 42.8% of cardiac anomalies [14]. These may include congenital heart defects, such as ventricular asymmetry and septal defects, which can significantly impact the fetal heart's functionality [15,16]. Secondly, the four-chamber view (with additional Doppler interrogation) might aid in evaluating the cardiac rhythm and the flow of blood within the heart chambers [13,17]. By observing the movements of the atrioventricular valves and the ventricular contractions, it becomes possible to assess the synchronization and efficiency of the cardiac cycle. Additionally, the visualization of the blood flow through the chambers aids in identifying any obstructions or abnormalities affecting the circulation, such as stenosis or regurgitation of valves. Lastly, the four-chamber view provides an opportunity to assess the overall development of the fetal heart. It allows for the measurement of key parameters like the size and contractility of all chambers, the thickness of the ventricular walls, and the integrity of normal anatomical structures like the interatrial and interventricular septa. These measurements will give important information regarding appropriate cardiac growth and development. Furthermore, the 4CV is instrumental in determining the position and orientation of the fetal heart in relation to the lungs within the chest cavity [18,19]. This information is crucial for diagnosing conditions like dextrocardia, where the heart is located on the right side of the chest instead of the left. Understanding the heart's position as well as the fetal cardiac axis is essential to facilitate accurate diagnosis and planning further management or interventions. An abnormal cardiac axis can be associated with CHD, and the likelihood of an abnormal cardiac axis depends on the CHD type [20,21].

The detection rate of congenital heart defects (CHDs) reportedly depends on several factors, and despite advances that have been made in recent years, it remains challenging to achieve satisfying detection rates. Possible explanations include a lack of routine prenatal screening, either by access to prenatal care or the absence of standardized protocols for routine prenatal screening. Additionally, ultrasound is an operator-dependent technology. The accuracy of CHD detection can depend on the expertise and experience of the healthcare professional performing and interpreting the diagnostic tests [22]. A recent meta-analysis revealed a detection rate of CHD of 45.1% in an unselected population, with an even higher rate among univentricular defects and heterotaxy of above 85% [23]. Rural residence and, therefore, limited access are associated with a decreased rate of prenatal diagnosis of major CHD and an increased risk of late diagnosis (≥22 gestational weeks) [24].

Still, some CHD cases remain undetected. The most commonly undiscovered CHD are conotruncal defects with a normal four-chamber view (TGA, Fallot's tetralogy, DORV, truncus arteriosus) [25]. With the advent of high-resolution ultrasound systems and AI-driven software solutions in the last decade, it has been suggested that four-dimensional ultrasound with spatiotemporal image correlation (STIC) might increase the detection rate of CHD [26–28]. Multiple computerized aids were developed to improve fetal echocardiography. Volume measurements applying 4D ultrasound facilitate virtual organ computer-aided analysis (VOCAL). With VOCAL ventricular volume, as well as total systolic volume, ejection fraction and cardiac output become assessable [29,30]. With SonoAVC or M-STIC, the

AV valve plane can be analyzed, assessing the mitral and/or tricuspid annular plane systolic excursion (MAPSE/TAPSE) [31,32]. ESTIC (electronic spatiotemporal image correlation) helps to optimize the acquisition time and image quality in 4D echocardiography [33]. Tomographic ultrasound imaging (TUI) or multi-slice view (MSV) creates image sections of the same plane, but it is limited to the actual plane and fails in cases where the cardiac axis is oriented differently [34,35].

Fetal intelligent navigation echocardiography (FINE) is an even more advanced approach: the software generates a virtual map of the STIC volume dataset, creating nine standard fetal echocardiographic views [36–39]. Additionally, automated measurements and calculations, such as the cardiac axis, can be performed. The abnormal cardiac axis is often the first hint of an underlying cardiac anatomic pathology. In complex CHD, including dextrocardia and situs solitus or left heart abnormalities, FINE can detect multiple abnormalities and define the complex anatomic relationship [28,40]. FINE has a high detection rate with a sensitivity of 98% and a specificity of 93% [40,41]. In the analysis from Yeo et al., CHD detected by FINE completely matched 74% of cases, with minor discrepancies in 12% and major discrepancies in 14% [42]. FINE has been demonstrated to be useful in the assessment of CHD [43]. Recently, FINE has been improved with a very rapid static volume acquisition, including a high frame rate or precise control of the cardiac plane along the x, y and z axis [42].

In this multicenter analysis, we aimed to scrutinize the utility of FINE in regard to the fetal cardiac axis in fetuses with CHD and healthy fetuses.

2. Materials and Methods

In this study, STIC volumes of fetal echocardiography of cases with CHD, thoracic masses, or situs ambiguus were identified and analyzed retrospectively between 2016 and 2018. As a control group, volumes of normal fetal hearts were utilized. STIC works by acquiring a series of 2D ultrasound images over several cardiac cycles. These images are obtained by volume ultrasound probe to capture different views of the fetal heart. The timing of the image acquisition is synchronized with the fetal heart rate to ensure consistency. Once the series of images is acquired, sophisticated software algorithms are applied to analyze and correlate the images. The software tracks and matches corresponding structures and features in each frame, taking into account their spatial position and temporal changes. By analyzing these correlations, a dynamic 4D model of the fetal heart and its movements is reconstructed. The FINE technique begins with a standard STIC volume acquisition. The operator identifies seven standardized landmarks (therefore, semi-automatic measurement). Based on these findings, a virtual map of the volume dataset is created. Finally, FINE semi-automatically generates and displays the nine standard fetal echocardiographic views by applying intelligent navigation technology to STIC datasets [36–39]. The FINE software can also perform automated measurements and calculations, such as the cardiac axis. The volumes were obtained by physicians applying a WS80A Elite US system (Samsung Medison, Seoul, Republic of Korea). The datasets were acquired from an apical four-chamber view using a mechanical convex transducer (1–8 MHz) by applying transverse sweeps through the fetal chest. The acquisition time was 10 to 12 s, with an acquisition angle from 20° to 35°.

The patient's consent was obtained in written form. Ethical approval was received from the ethics committee of Charité University Hospital on 21 April 2016 (EA2/066/16). CHD cases that were included in this study were hypoplastic left heart syndrome (HLHS, $n = 157$), atrioventricular septal defect (AVSD, $n = 75$), double outlet right ventricle (DORV, $n = 87$), as well as other major CHD and rare CHD. Additionally, cases with rhabdomyoma ($n = 9$), thoracic masses ($n = 11$), and situs ambiguus ($n = 15$) were included. Initially the STIC volume was generated. Following the generation of seven anatomical planes, the FINE software semi-automatically created nine echocardiography standard planes based on the ISUOG and AIUM guidelines. Additionally, the cardiac axis was calculated automatically. The STIC images were generated at the two prenatal centers (Lübeck and Berlin, Germany).

Statistical analysis was conducted using GraphPad Prism 9 for Mac (Version 9.51, GraphPad Software Inc., La Jolla, CA, USA), GraphPad QuickCalcs (GraphPad Software Inc., La Jolla, CA, USA), and Microsoft Excel for Mac (Version 16.71, Microsoft Corp., Redmond, WA, USA). Descriptive statistics, *t*-tests, McNemar tests, and Kruskal–Wallis tests were applied. A p-value of < 0.05 was assumed to be significant.

3. Results

Five hundred forty-five volumes of CHD or thoracic masses were included and compared to 1543 normal fetal hearts. The median of the normal fetal cardiac axis is between 40 and 45° [18,44] (Figure 1). The different types of CHD and the thoracic masses/anomalies are listed in Table 1, as well as the distribution among the measured volumes (mean, median, range). Among the 545 volumes obtained from CHD or thoracic masses cases, there were 7 volumes of the absent pulmonary valve, 5 of aortic stenosis, 5 of atrioseptal defect (ASD), 75 of atrioventricular septal defect (AVSD), 20 of coarctation aortae, 20 of complex CHD, 2 of double aortic arch (DAA), 87 of double outlet right ventricle (DORV), 157 of hypoplastic left heart syndrome (HLHS), 27 of hypoplastic right heart syndrome (HRHS), 1 of interrupted aortic arch (IAA), 19 of other CHD, 19 of pulmonary atresia, 12 of right aortic arch (RAA), 5 of rhabdomyoma, 15 of situs ambiguus (heterotaxy), 30 of transverse aortic constriction (TAC), 21 of transposition of the great arteries (TGA), 25 of tetralogy of Fallot (TOF), as well as 11 of thoracic masses. In 86% (471 out of 545 volumes), an abnormal cardiac axis was detected. Median and interquartile ranges of the cardiac axis were assessed by the FINE software (Figures 1–4). Of note, situs ambiguous (heterotaxy) refers to the abnormal position of thoracic and visceral organs but does not necessarily imply a specific type of CHD. The cardiac axis in CHD cases was compared to the control. In CHDs such as absent pulmonary valve, aortic stenosis, ASD, pulmonary atresia, TOF, and complex CHD, the cardiac axis was >45°. In CHD such as RAA, situs ambiguus the heart axis appeared to be <20°. CHDs such as HRHS, situs ambiguous, and TGA displayed a high range of the cardiac axis. Kruskal–Wallis test showed a significant deviation from the normal fetal heart axis in cases of HLHS, pulmonary atresia, TOF (p-value < 0.0001), RAA, situs ambiguus (p-value = 0.0001–0.001) absent pulmonary valve syndrome, DORV, thoracic masses (p-value = 0.001–0.01).

Table 1. Distribution of the fetal cardiac axis measurements in fetuses with CHD/thoracic masses using FINE. Kruskal–Wallis test showed a significant deviation from the normal fetal heart axis in cases of HLHS, pulmonary atresia, TOF (**** p-value < 0.0001), RAA, situs ambiguus (*** p-value = 0.0001–0.001) absent pulmonary valve syndrome, DORV, thoracic masses (** p-value = 0.001–0.01).

CHD/Thoracic Mass	n	Axis Mean (Range)	Axis Median
Absent pulmonary valve **	7	64.0° (38.5–76.2°)	68.6°
Aortic stenosis	5	49.4° (34.2–60.1°)	50.3°
ASD	5	50.6° (45.3–57.4°)	48.9°
AVSD	75	40.0° (19.5–66.9°)	40.5°
Coarctation aortae	20	39.2° (30.7–55.0°)	38.8°
Complex CHD	8	47.1° (22.9–78.2°)	48.1°
DAA	2	39.2° (36.8–41.7°)	39.2°
DORV **	87	45.9° (8.7–105.4°)	43.2°

Table 1. *Cont.*

CHD/Thoracic Mass	n	Axis Mean (Range)	Axis Median
HLHS ****	157	45.1° (10.2–87.2°)	45.8°
HRHS	27	32.1° (−54.8–65.7°)	49.6°
IAA	1	45.6°	45.6°
Others	13	34.8° (19.9–46.2°)	37.3°
Pulmonary Atresia ****	19	60.2° (26.6–97.0°)	61.5°
RAA ***	12	24.1° (15.3–39.0°)	23.8°
Rhabdomyoma	5	37.7° (28.3–58.5°)	34.2°
Situs ambiguus	15	−8.0° (−31.4–36.7)	−16.8
TAC ***	30	50.3° (24.4–65.7°)	51.6°
TGA	21	34.6° (−3.7–69.6°)	34.8°
TOF ****	25	56.6° (29.4–86.9°)	58.9°
Thoracic masses	11	23.3° (13.4–48.9°)	21.8°
Total	545		

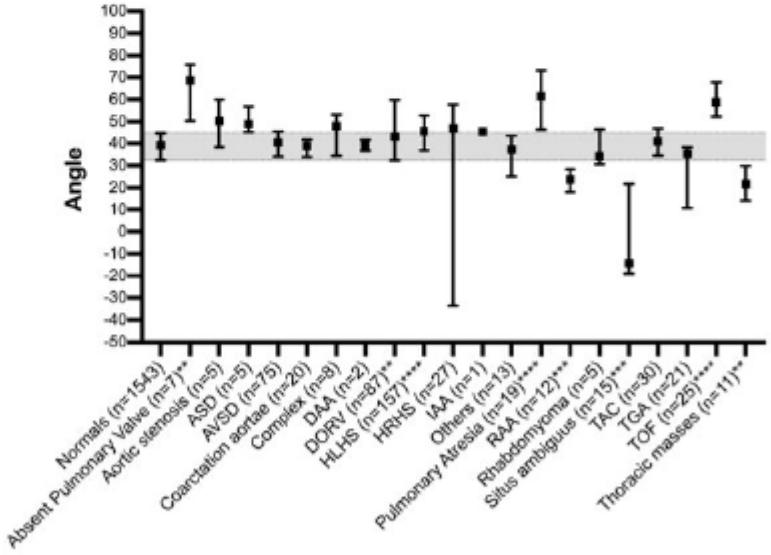

Figure 1. Median and interquartile ranges of the cardiac axis assessed by FINE. The broad grey line indicates the normal fetal cardiac axis is 40–45°. Note that CHDs such as absent pulmonary valve, aortic stenosis, ASD, pulmonary atresia, TOF, and complex CHD display a cardiac axis of >45°. In CHD such as RAA, situs ambiguus the heart axis appears to be <20°. CHDs such as HRHS, situs ambiguous, and TGA display a high range of the cardiac axis. Kruskal–Wallistest with multiple comparisons vs. normal, significance with adjusted *p*-values: HLHS, pulmonary atresia, TOF *p*-value < 0.0001; RAA, situs ambiguus *p*-value = 0.0001–0.001; absent pulmonary valve syndrome, DORV, thoracic masses 0.001–0.01.

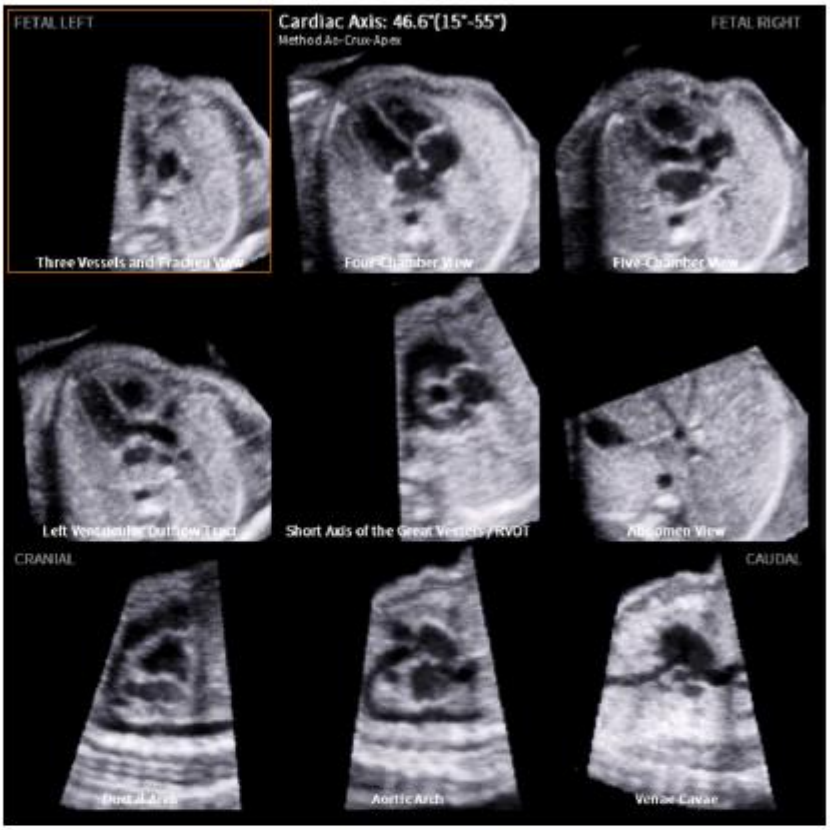

Figure 2. Example of fetal intelligent navigation echocardiography (FINE): a normal fetal heart with a computerized cardiac axis of 46.6°. All nine planes are depicted (from left to right): three vessels and trachea view, four-chamber view, five-chamber view, left ventricular outflow tract, the short axis of the great vessels (right ventricular outflow tract), abdomen view, ductal arch, aortic arch and venae cavae.

Figure 2 visualizes the structured analysis of all nine planes in a fetus with normal cardiac anatomy: three vessels and trachea view, four-chamber view, five-chamber view, left ventricular outflow tract, the short axis of the great vessels (right ventricular outflow tract), abdomen view, ductal arch, aortic arch and venae cavae. The cardiac axis is calculated at 46.6°. In contrast, Figure 3 depicts a case of double inlet left ventricle (DILV) with pulmonary valve atresia with a cardiac axis of 67.5°. In this case, FINE is able to visualize the pathology that affects different cardiac planes in one examination. The three vessels and trachea view show the absence of the truncus pulmonalis. The four-chamber view reveals the non-appearance of the ventricular septum. Additionally, the right ventricular outflow tract and ductal arch indicates further the pulmonary valve atresia and stenosis of the truncus pulmonalis. Simply looking at the four-chamber views and cardiac axis obtained by FINE (Figure 4) underlines how effective and advanced this approach is. In Figure 4, various CHD and thoracic anomalies are depicted in comparison to the normal fetal heart—in most cases, the abnormal cardiac axis becomes apparent.

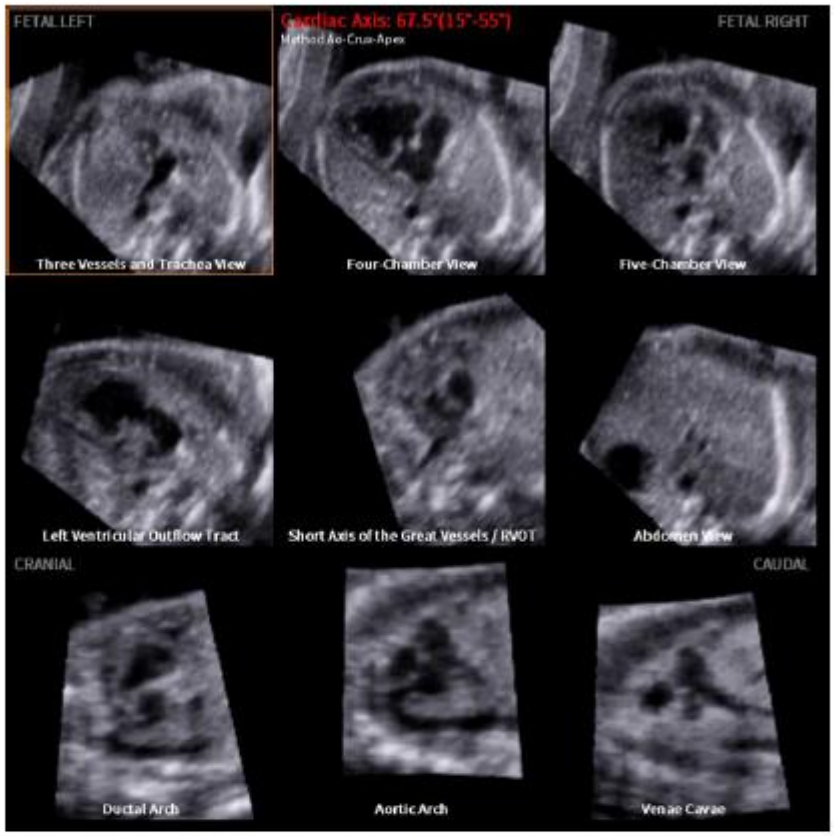

Figure 3. Example of fetal intelligent navigation echocardiography (FINE): the images display a fetus's heart with a double inlet left ventricle (DILV) and pulmonary valve atresia, with a computerized cardiac axis of 67.5°. All nine planes are depicted (from left to right): three vessels and trachea view—with an absent truncus pulmonalis, four-chamber view—with the absence of the ventricular septum, five-chamber view, left ventricular outflow tract, the short axis of the great vessels (right ventricular outflow tract)—with an absent truncus pulmonalis, abdomen view, ductal arch—which does not become visible, aortic arch and venae cavae.

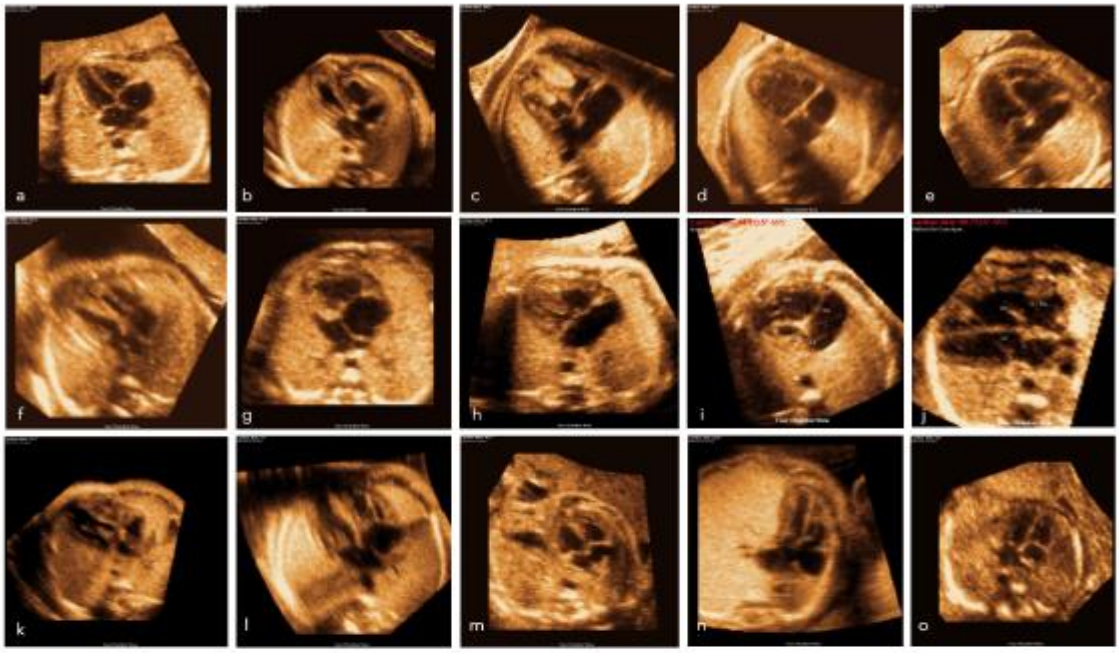

Figure 4. Images of the four-chamber view of a normal fetal heart (**a**) and examples of CHD and thoracic abnormalities from our cohort (**b**–**o**). (**b**) Coarctation aortae, (**c**) rhabdomyoma, (**d**) DILV, (**e**) Ebstein, (**f**) coarctation aortae, (**g**) HLHS, (**h**) AVSD, (**i**) HLHS, (**j**) tetralogy of Fallot, (**k**) HRHS, (**l**) RAA, m: diaphragmatic hernia, (**n**) CPAM, (**o**) situs ambiguus (heterotaxy).

4. Discussion

The present study is able to demonstrate that FINE is a good tool to assess the fetal cardiac axis during a standardized semi-automated fetal echocardiography (Figures 2–4). Fetal intelligent navigation echocardiography (FINE) has been developed to interrogate STIC volume datasets by applying an "intelligent navigation" technology. It facilitates the automatic display of nine standard fetal echocardiography views that are required to diagnose most cardiac defects (Figures 2–4). This analysis highlights the importance of assessing the fetal cardiac axis and depicts the high range and or/deviation of the cardiac axis in fetuses with CHD or thoracic anomalies compared to healthy control. So far, this is the first study which focuses on the cardiac axis in a wide range of CHD and other thoracic pathologies. The fetal cardiac axis in normal controls ranges mainly between 40 and 45° (normal range 15–55°), which was confirmed in our healthy controls (Figure 1). In 86% (471 of 542 volumes) of our pathological cases, an abnormal cardiac axis was detected. Interestingly, CHDs such as absent pulmonary valve, aortic stenosis, ASD, pulmonary atresia, TOF, and complex CHD display a cardiac axis of >45°. In CHD such as RAA, situs ambiguus the heart axis appears to be <20°. It is of note that CHD, like HRHS, situs ambiguous, and TGA display a high range of the cardiac axis. Significant differences between the fetal axis in the normal heart versus CHD were detected in HLHS, pulmonary atresia, TOF (p-value < 0.0001), RAA, situs ambiguus (p-value = 0.0001–0.001), and absent pulmonary valve syndrome, DORV, thoracic masses (p-value = 0.001–0.01).

Our data are in accordance with other recent studies, which were able to demonstrate that FINE is a good tool to accurately diagnose CHD. An abnormal fetal cardiac axis can point towards CHD and promote an early diagnosis [40–43]. A recent analysis was able to demonstrate that the cardiac axis is significantly different from the normal axis in conotruncal anomalies (DORV, TAC, and TOF) [45]. Additionally, the study showed that in fetuses

with TGA, the fetal cardiac axis does not differ compared to the normal axis. The group suggests the evaluation of the fetal cardiac axis, especially in screening for conotruncal anomalies. Several studies were able to demonstrate that the evaluation of the fetal cardiac axis can be an additional helpful tool in the prenatal diagnosis of CHD. Zhao et al. were able to reveal a correlation between neonatal death and an abnormal fetal cardiac axis in fetuses with tetralogy of Fallot [46]. They argued that an abnormal cardiac axis is associated with pulmonary atresia, right-sided aortic arch, and, therefore, a more complicated form of tetralogy of Fallot, which explains the higher risk of adverse neonatal outcome. A recent analysis suggests that a fetal cardiac axis is an additional tool for screening for CHD and fetal aneuploidy during the first-trimester scan [47]. They calculated a sensitivity of the fetal cardiac axis of 50.0% for CHD and 41.2% for fetal aneuploidy. Additionally, the cardiac axis can also be measured with fetal MRI when dedicated ultrasound and echocardiography are technically limited due to different aspects (e.g., BMI, multiples, fetal position). Liu et al. demonstrated that the cardiac axis measurement by fetal cardiac MRI is coherent to the sonographic cardiac axis evaluation [21].

An abnormal fetal cardiac axis should raise concerns for CHD or other fetal anomalies. FINE might be a reliable method to facilitate prenatal diagnosis of CHD and benefit counseling parents and professionals on decision-making on the pregnancy and follow-up of the fetus. With an early and accurate diagnosis, FINE might improve neonatal outcomes. It is possible to simply analyze the fetal cardiac axis with FINE. This tool is applicable to remote areas where sonographic training is limited [22].

This study is limited by the retrospective nature of the analysis and a selection bias, as not all patients who presented at the centers during the study period obtained a 3D ultrasound, including STIC volume. The volumes were generated by ultrasound experts, so the image and data quality are high.

5. Conclusions

This study reveals that the cardiac axis very likely deviates from CHD and varies depending on the type of underlying cardiac pathology. Especially in fetuses with HLHS, pulmonary atresia, TOF (p-value < 0.0001), RAA, situs ambiguus (p-value = 0.0001–0.001), and absent pulmonary valve syndrome, DORV, thoracic masses (p-value = 0.001–0.01) the fetal cardiac axis was significantly different from normal heart. An abnormal fetal cardiac axis should raise the suspicion of an underlying CHD.

The results confirm that FINE is a valuable tool for accurate, standardized detection and identification of CHD. Beyond that, our data show that combining the results with a semi-automatic assessment of the cardiac axis might improve the detection rate of fetuses with CHD. The evaluation of the fetal cardiac axis is an essential part of fetal echocardiography as it can facilitate the detection of CHD.

The information yield from FINE depends on the examiner's scanning skills and image optimization, as well as the examiner's expertise and experience in this field. Therefore, further teaching of FINE in prenatal diagnosis worldwide to improve the skills and experience of the examiners improves early detection and assessment of CHD and could possibly improve fetal outcomes. In conclusion, FINE will aid in improving the prenatal diagnosis and assessment of CHD as well as other stressful conditions in utero.

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3. Diskussion

Die Geburtsmedizin bietet in vielerlei Hinsicht eine personalisierte Betreuung, die sich nach dem individuellen Risikoprofil der Schwangeren und des Kindes richtet. Die durch die Mutterschaftsrichtlinien vorgesehenen Untersuchungen haben unter anderem das Ziel der frühzeitigen Risikofeststellung und angemessene Schwangerschaftsvorsorge. Zahlreiche Möglichkeiten der risikoadaptierten Anpassung der Betreuung einer Schwangeren während der Vorsorgen (Gewichtszunahme und Gestationsdiabetes) und peripartal (Zervixreifung bei Frauen mit einem Kaiserschnitt in der Vorgeschichte und im ambulanten Setting) werden in dieser Arbeit beleuchtet.

Ein elementarer Bestandteil der Schwangerenvorsorge und Risikoerkennung ist die pränatale Diagnostik, welche unter anderem eine strukturierte fetale Screening Untersuchung einschließlich der Plazentabeurteilung und Überprüfung der Durchblutungsverhältnisse beinhaltet.

Die drei Ultraschalluntersuchungen, die durch die Mutterschaftsrichtlinien vorgesehen sind, werden allen gesetzlich-versicherten Schwangeren angeboten. Nach der letzten Novellierung am 01.07.2013 durch den Gemeinsamen Bundesausschuss hat die Schwangere bei der Ultraschalluntersuchung im zweiten Trimenon die Wahl zwischen zwei Optionen, um eventuelle Auffälligkeiten zu erkennen, nämlich der „Basis-Ultraschalluntersuchung“ (im Wesentlichen fetale Biometrie und Plazentaposition) und der „erweiterten Basis-Ultraschalluntersuchung“, das so genannte IIb Screening (1). Es sieht eine systematische Sonographie mit Beurteilung der fetalen Morphologie durch eine qualifizierte Person vor. Das IIb Screening wird zwischen 18+0 und 21+6 SSW durchgeführt. Die Qualifizierung kann mittels Online Seminar und Test erfolgen. Schmand et al. haben in Hessen untersucht, wie sich die Detektionsrate von fetalen Fehlbildungen zwischen 2010 und 2016 nach Einführung des IIb Screening durch den Gemeinsamen Bundesausschluss am 01.07.2013 verändert hat (101). Vor der Einführung lag die Detektionsrate bei 25,5% und bei 24,9% nach 2013. Trotz Einführung der erweiterten Screening Untersuchung hat sich die Rate an vorgeburtlich festgestellten Fehlbildungen nicht verringert. Die AutorInnen schlagen einen alternativen Ansatz zur besseren Detektion fetaler Malformationen vor: Eine strukturierte und umfangreiche Screening Untersuchung durch ExpertInnen der Pränataldiagnostik (Ersttrimesterscreening, Feindiagnostik), womit eine eingehende systematische

Untersuchung des Fetus auf hohem Niveau und einen entsprechend höhere Detektionsrate von fetalen Fehlbildungen gewährleistet ist (1.3 Pränataldiagnostik – angebotene Untersuchungen und mögliche weiterführende Diagnostik).

Eine Möglichkeit der Intensivierung und Unterstützung der strukturierten fetalen Screening Untersuchung bietet ebenfalls die Anwendung von Künstlicher Intelligenz (KI). Der Einsatz von KI erleichtert den Ablauf der Untersuchung, sowie die Erkennung und Beurteilung von Befunden (3.1 Künstliche Intelligenz in der Pränataldiagnostik). Auch die weiterführende Diagnostik bei fetalen Fehlbildungen ist komplex und bietet stufenweise genetische Untersuchungen von der Beurteilung des Chromosomensatzes bis hin zu exakten Kodierungen von Genen (3.2 Evolution der genetischen Diagnostik in der Pränataldiagnostik). Auch hier ist eine stufenweise Intensivierung der Diagnostik je nach Befund eine Option um die Detektionsrate von genetischen Aberrationen zu verbessern. Auf diese zwei Aspekte wird in den folgenden Kapiteln eingegangen.

3.1. Künstliche Intelligenz in der Pränataldiagnostik

Künstliche Intelligenz (KI) bezieht sich auf die Möglichkeit, Daten zu interpretieren und durch flexible Adaption zu lernen (Deep Learning) (102). Sie ist bereits fester Bestandteil in der Radiologie. In der sonographischen Diagnostik von Leber, Schilddrüse und Mamma zeigte sich die Anwendung von KI als erfolgversprechend (103, 104). Auch die Pränataldiagnostik ist ein Feld, das von KI profitiert (Abbildung 10). Durch die zügige Messung von Strukturen und die automatisierte Einstellung von Ebenen kann Zeit gespart und die Untersuchung effektiv gestaltet werden (105-107). Die Entlastung von aufwendiger Bildeinstellung und manueller Strukturmessung kann zur Fokusverlagerung der untersuchenden Person auf die eigentliche Interpretation der Aufnahme beitragen und somit die Diagnostik erleichtern.

Zahlreiche Aspekte der Pränataldiagnostik bieten Anwendungsmöglichkeiten für KI (Abbildung 10). Im ersten Trimenon kann die Messung des Gestationssacks sowie von Standardebenen im Rahmen des ETS (Erkennung und Messung von fetalen Strukturen, Nackentransparenz) durch KI erleichtert werden (108-110). Im zweiten Trimester steht die Messung von verschiedenen Bildebenen zur Beurteilung von fetalen Fehlbildungen im Vordergrund. Durch die automatisierte Erkennung und Messung der Standardeinstellungen

kann der Workflow erleichtert und Zeit gespart werden. Zusätzlich reduziert die automatisierte Messung bei optimalen Voraussetzungen den Untersucher-Bias und resultiert in objektiven Messwerten. Die Beurteilung des fetalen Kopfumfangs sowie der Strukturen des zentralen Nervensystems ist bereits etabliert (111). Die automatisierte Messung findet ebenfalls beim fetalen Abdomen und bei den langen Röhrenknochen Anwendung (112).

In der Echokardiographie wurden verschiedene Anwendungen zur automatisierten Erkennung, Generierung der Standardebenen und Diagnostik entwickelt. Kongenitale Herzfehler sind die häufigsten organbezogenen Fehlbildungen mit 8 bis 10 per 1000 Lebendgeburten (0,8 bis 1 %) (113, 114). Die pränatale Diagnose eines Herzfehlers erleichtert die Beratung der Eltern und führt zu einer Reduktion der kindlichen Mortalität (96). Die Beurteilung des fetalen Herzens kann durch automatisierte Volumenaufnahmen, zum Beispiel durch STIC (Spatiotemporal Image Correlation), erleichtert werden (Abbildung 9). Die Beurteilung der Atrioventrikularklappen-Ebene (MAPSE/TAPSE, Mitral and/or Tricuspid Annular Plane Systolic Excursion) ist durch SonoAVC beim Feten analog zur Echokardiographie für Erwachsene möglich (115, 116). Eine Erweiterung der computerisierten automatischen Messung stellt FINE dar. Mit dieser Anwendung werden STIC-Volumina von einer intelligenten Navigationstechnologie analysiert. Dadurch können die neun vorgesehenen Standard-Echokardiographie-Ebenen generiert und analysiert werden (117-122). FINE dient zur Unterstützung der standardisierten fetalen Echokardiographie und der Diagnose von fetalen Herzfehlern (Abbildung 9, Kapitel 2.5). Eine aktuelle Arbeit zur automatisierten Messung der fetalen Herzachse mit FINE konnte zeigen, dass eine Abweichung der Herzachse mit dem Vorhandensein von kongenitalen Herzfehlern korreliert (123).

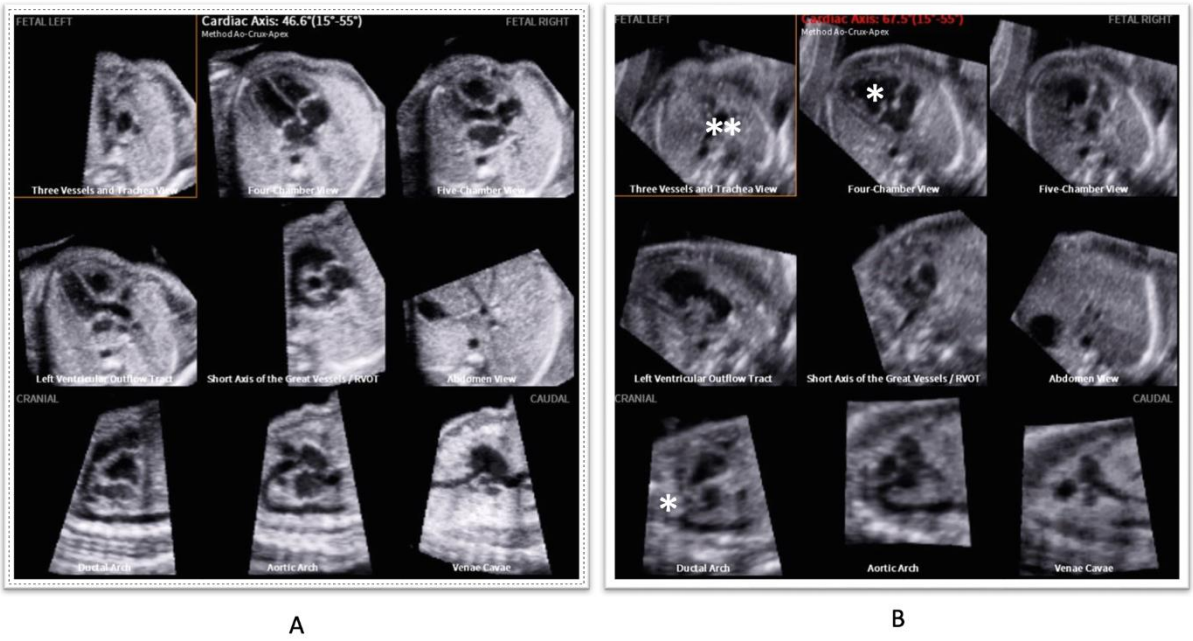

Abbildung 7: *Fetal Intelligent Navigation Echocardiography (FINE) (Abbildungen von der Autorin). A: Aufnahme eines unauffälligen fetalen Herzens mit neun Standardebenen (von links oben nach rechts: Dreigefäßblick, Vierkammerblick, Fünfkammerblick, linksventrikulärer Ausflusstrakt, kurze Achse der großen Gefäße, Abdomen, Duktusbogen, Aortenbogen, bikavale Ansicht). Die Herzachse ist bei 46,6° im normalen Range. B: Echokardiographie bei einem Feten mit Double Inlet Left Ventricle (DILV) und Pulmonalatresie. Der Dreigefäßblick weist in diesem Fall nur zwei große Gefäße auf (*Aorta und *Vena cava superior), der Vierkammerblick und der linksventrikuläre Ausflusstrakt deuten auf die *Abwesenheit des Ventrikelseptums hin, bei der Aufnahme des Duktusbogens fällt die *Pulmonalatresie auf.*

Die Verwendung von KI kann die Diagnose fetaler Fehlbildungen erleichtern. Ein Deep-Learning-Modell weist eine Überlegenheit in der Detektion von Trisomie 21 im ETS gegenüber der konventionellen Kombination von Nackentransparenzmessung und mütterlichem Alter auf (124). Das fetale Profil kann durch Deep-Learning-Module analysiert werden und Hinweise darauf geben, ob eine genetische Aberration vorliegt und um welche es sich handeln könnte (125). In der Analyse des fetalen zentralen Nervensystems kann das PAICS (Prenatal ultrasound diagnosis Artificial Intelligence Conduct System) dabei unterstützen, effektiv und auf hohem Niveau Bilddaten zu analysieren und zerebrale Pathologien zu diagnostizieren (126). Eine KI-basierte Analyse fetaler Messwerte und Aufnahmen kann die Diagnose einer fetalen Pathologie (zum Beispiel von Syndromen) erleichtern (127).

Insgesamt verspricht KI eine Erleichterung des Workflows in der Pränataldiagnostik (Abbildung 10). Unter optimalen Sichtbedingungen werden eine objektive Messung und Beurteilung von potentiellen Pathologien ermöglicht. Die Entwicklungen und Verbesserungen von KI-Anwendungen in der Pränataldiagnostik setzen sich fort. Die Reichweite und die Zugänglichkeit der KI sind abhängig vom Training der Untersuchenden und den technischen Voraussetzungen der jeweiligen Einrichtung.

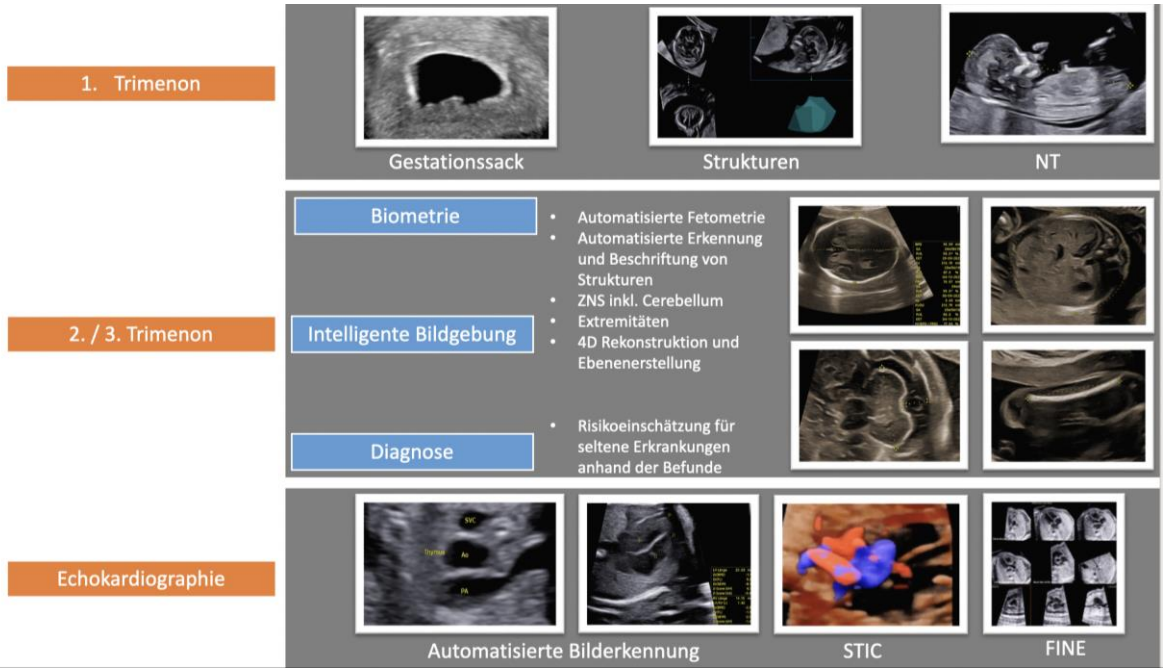

Abbildung 8: *Verschiedene Möglichkeiten der Anwendung von KI in der Pränataldiagnostik (Grafik von der Autorin). Die Anwendungsbeispiele sind hier in Bezug auf das erste Trimester bzw. das zweite und dritte Trimester sowie in der fetalen Echokardiographie dargestellt. Im ersten und zweiten Trimester kann KI vor allem dabei unterstützen, automatisch Strukturen zu erkennen und zu messen. Verschiedene Softwareprodukte wurden entwickelt, um die Befunde des Ultraschalls zu analysieren und spezifisch Risiken für fetale Erkrankungen aufzuzeigen. In der Echokardiographie kann KI genutzt werden, um automatisiert Strukturen zu beschriften und zu messen. Über 3D-Volumina gemeinsam mit einer Software können Standardebenen der fetalen Echokardiographie erstellt und analysiert werden. FINE = Fetal Intelligent Navigation Echocardiography, STIC = Spatiotemporal Image Correlation.*

3.2. Evolution der genetischen Diagnostik in der Pränataldiagnostik

Die genetische Diagnostik war schon von Anfang an ein Teil der Pränataldiagnostik und geht auch heute noch Hand in Hand mit der vorgeburtlichen Ultraschalluntersuchung. Zunächst stand die Fruchtwasseruntersuchung zur Feststellung von chromosomalen Aberrationen sowie von Rhesusinkompatibilät im Fokus (128, 129). Initial erfolgte vor allem die Kultivierung der Amniozyten. Es wurde eine konventionelle Zytogenetik mit Bestimmung des fetalen Karyotyps durchgeführt (130). Über die Jahrzehnte wurde eine komplexe Diagnostik zur Detektion von submikroskopischen Veränderungen entwickelt (131). In den späten 1970er Jahren konnte dann die molekulare Diagnostik in der Genetik ausgearbeitet werden, initial zur Diagnose der Hämoglobinopathien (132). Noch vor 20 Jahren wurde Frauen mit einem fortgeschrittenen mütterlichen Alter routinemäßig eine Amniozentese zum Ausschluss einer Trisomie 21 angeboten. Heute ist die Diagnostik bezüglich des Down-Syndroms zum Teil durch den NIPT abgelöst worden (133). Dies zeigt sich in der Anzahl der invasiven Eingriffe: Diese ist in den letzten Jahren vermutlich durch diesen Effekt drastisch gesunken. 2012 erhielten noch 20 639 Schwangere in Deutschland eine Amniozentese, 2018 waren es nur 8538 Schwangere.

Der Fokus hat sich vom Ausschluss eines Down-Syndroms zur Detektion fetaler Fehlbildungen und anderer geburtsmedizinisch relevanter Befunde verschoben. Fetale Fehlbildungen können in 2 bis 4 % aller Schwangerschaften diagnostiziert werden (19, 20). Je nach Befund kann es dafür unterschiedliche Ursachen geben: genetische, metabolische, infektiöse, teratogene und ungeklärte. Im Falle der pränatalen Diagnose einer fetalen Malformation wird unter anderem eine genetische Beratung angeboten, um mit Hilfe der Einschätzung von GenetikerInnen die Fehlbildung kontextuell einzuordnen und das Thema der weiteren Diagnostik zu beurteilen (134). Mögliche diagnostische Prozeduren zur Gewinnung von fetalen bzw. plazentaren Zellen sind je nach Schwangerschaftsalter und spezifischem Befund die Chorionzottenbiopsie, die Amniozentese, die Cordozentese und die Plazentapunktion. Zu den Indikationen gehören: der Verdacht auf eine fetale Chromosomenanomalie, ein erhöhtes Risiko für eine bekannte genetische oder biochemische Erkrankung des Fetus, v. a. bei fetaler Infektion, und psychische Gründe (Angst vor einer Chromosomenanomalie des Fetus) (134).

Durch die komplexe Entwicklung in der Zytogenetik und der Molekularbiologie hat sich der Umfang an Möglichkeiten zur Diagnostik genetischer Varianten enorm vergrößert (27). Bei

Verdacht auf eine genetische Erkrankung erfolgt eine stufenweise diagnostische Abklärung (Abbildung 2, 10). Zunächst erfolgt die Evaluation des Karyotyps, dies kann durch den NIPT oder durch invasive Methoden erfolgen. Sollte der fetale Karyotyp unauffällig sein, können weiterführende Analysen erfolgen. Besteht der Hinweis auf eine Mikrodeletion oder -duplikation (Copy Number Variant = CNV), kann ein Microarray durchgeführt werden (zum Beispiel bei Verdacht auf DiGeorge-Syndrom) (135, 136). Dabei werden Strukturvarianten und submikrosokopische chromosomale Veränderungen analysiert. Sollte der Mirkoarray unauffällig sein, kann eine Exom-Sequenzierung erfolgen, meist wird diese aus dem genetischen Material von dem ungeborenen Kind, sowie der Eltern generiert (Trioexom). Die Exom-Sequenzierung bezieht sich ausschließlich auf die Analyse von Exomen oder Protein-kodierenden Regionen des Genoms (137). Exome kodieren 22 000 Gene und erfassen 1,5 % der menschlichen DNA (138). Die Geschwindigkeit und Effektivität der Sequenzierung hat in den letzten Jahren deutlich zugenommen (30, 138-140). Einige Studien diskutieren die schrittweise Ablösung und Ersetzung des Mikroarrays durch die Genomsequenzierung (Whole Genome Sequencing). Die Genomsequenzierung kann das vollständige Genom beurteilen, also Exons und Introns (24).

Zahlreiche aktuelle Untersuchungen beziehen sich auf die Frage, wie häufig genetische Aberrationen bei einem auffälligen fetalen Phänotyp detektiert werden. Eine aktuelle Analyse einer Trioexom-Datenbank zeigte, dass nach einem unauffälligen Karyotyp insgesamt 38 % der pränatal diagnostizierten Fehlbildungen durch die Molekulargenetik erklärt werden können (Abbildung 11). In 47,1 % der auffälligen Trioexom-Analysen wurde eine De-novo-Variante identifiziert. Bei 29,1 % der Feten konnte eine autosomal rezessive Genvariante diagnostiziert werden und bei 12,7 % zeigte sich eine parentale Vererbung (X-linked oder autosomal dominant). Andere Formen der Vererbung waren deutlich seltener (wie mitochondrial oder Deletion/Duplikation). Diese Analyse verdeutlicht, dass eine De-novo-Variante eine der häufigsten Ursachen in der pränatalen genetischen Diagnose von fetalen Fehlbildungen ist (141).

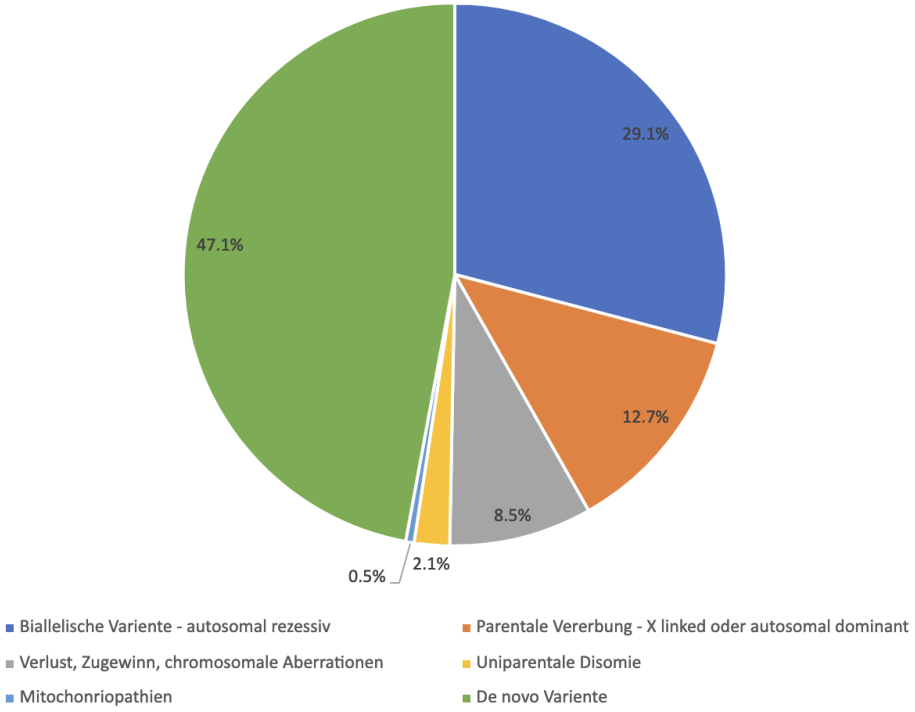

Abbildung 9: *Häufigkeitsverteilung der genetischen Varianten in einer Kohorte von 500 pränataldiagnostisch auffälligen Feten (Grafik von der Autorin). Bei 189 der 500 Feten (37,8 %) wurde eine genetische Variante diagnostiziert. In 47,1 % der Fälle zeigte sich eine De-novo-Variante (141).*

Im Hinblick auf spezifische sonographische Befunde scheint die weitere genetische Diagnostik bei einem unauffälligem Karyotyp relevante Zusatzinformationen zu liefern. Dieser Zusatzgewinn an Informationen (Incremental Yield) ist abhängig vom fetalen Phänotyp (Abbildung 12). Eine Metaanalyse hat gezeigt, dass die Exom-Sequenzierung 4 % an Zusatzinformationen bei Feten mit einer alleinigen Wachstumsrestriktion (IUGR), 30 % bei einem IUGR-Fetus mit zusätzlichen Anomalien, 48 % bei isoliert verkürzten Röhrenknochen und 68 % bei verkürzten Röhrenknochen und anderen Skelettanomalien liefern kann (142, 143). Eine aktuelle Analyse konnte zeigen, dass bei fetalen Nierenfehlbildungen das Trioexom in 52,6 % der Feten mit renalen Fehlbildungen und extra-renalen Anomalien eine pathogene Variante aufweisen (144). Auch bei pränatal diagnostizierten Fehlbildungen des zentralen Nervensystems hat die Exom-Sequenzierung eine große Bedeutung. Vor allem bei Feten mit Anomalien des zentralen Nervensystems und mit extra-zerebralen Fehlbildungen ist die Detektionsrate von pathologischen Varianten besonders hoch (35,7 % vs. 14,5 % in Feten mit isolierten Anomalien des zentralen Nervensystems) (145). Die weit verbreitete Trioexom-

Analyse löst die vorher häufig angewandte Panel-Analyse zunehmend ab (146). Bei der gezielten Panel-Analyse werden spezifische Gene untersucht, die bei bestimmten fetalen Fehlbildungen (zum Beispiel kongenitalem Herzfehler, Zwerchfellhernie und anderen) relevant sein können (147-150). In der Exom-Analyse werden 30-mal mehr Exome analysiert als bei der alleinigen Panel-Analyse.

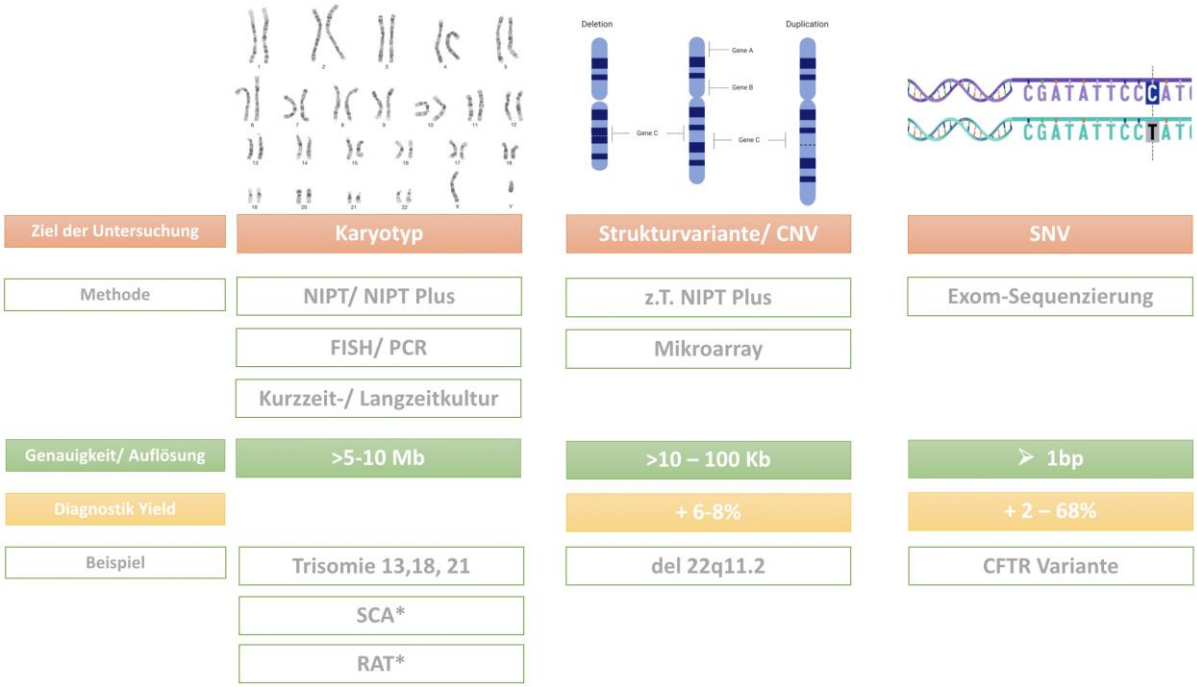

Abbildung 10: *Auswahl der gängigsten genetischen Analysen mit Darstellung des Untersuchungsgegenstands (roter Balken), der jeweiligen Auflösung (grüner Balken) und des Zusatzgewinns an Informationen (gelber Balken). Von links nach rechts. Grafik von der Autorin. Der fetale Karyotyp kann mittels NIPT oder invasiv gewonnen werden. Es werden Gengrößen >5–10 Megabasen beurteilt. Es können auch SCA (Sex Chromosome Aneuploidy), RAT (Rare Autosomal Trisomy) beurteilt werden. Strukturvarianten bzw. CNV können mit dem erweiterten NIPT zum Teil oder mit dem Mikroarray im Größenbereich >10-100 Kilobasen beurteilt werden. Der Zusatzgewinn an Informationen bei einem negativen Karyotyp kann 6–8 % sein. Monogene Erkrankungen/Single Nucleotide Variants betreffen meist eine Aminosäure in einem Exon. Die Analyse erfolgt durch die Exom-Sequenzierung. Je nach fetalem Phänotyp beträgt der Zugewinn an Informationen nach einem unauffälligen Karyotyp und Mikroarray 2–68 % (24, 25, 151, 152). *eingeschränkte Beurteilung durch den NIPT Plus. NIPT Plus = NIPT*

Die rapide Entwicklung in der pränatalen Genetik zeigt, wie relevant die Molekulargenetik für die Erkennung und Beurteilung von pränatalen Anomalien ist und was für einen Einfluss sie in der Beratung der Eltern bezüglich zukünftiger Schwangerschaften haben kann (141, 153).

Die durchschnittliche Bearbeitungszeit (Turnaround Time) liegt aktuell bei zwölf Tagen (Zentrum für Humangenetik Tübingen). Sollte bei einem Fetus ein auffälliger genetischer Befund detektiert werden, ist es essentiell, den werdenden Eltern eine interdisziplinäre Beratung mit GenetikerInnen, NeonatologInnen und ggf. KollegInnen aus spezifischen Fachdisziplinen sowie PsychologInnen anzubieten. Erst nach der Beratung ist eine informierte Entscheidung bezüglich des weiteren Schwangerschaftsverlaufs möglich. Das häufige Vorliegen einer De-novo-Variante ist für die Beratung der Eltern auch bei schweren fetalen Malformationen ein gewisser Trost, da die Chance eines erneuten Auftretens eher gering ist. Durch die genetische Diagnostik können auch bisher unbekannte Befunde erstellt werden, die zum Teil einen unklaren Einfluss haben (zum Beispiel VUS = Variant of Unknown Significance) (154, 155). Die Limitation in der Interpretation von VUS bedarf einer Aufklärung der Eltern. Die Belastung durch unklare Befunde sollte nicht unterschätzt werden (156).

4. Zusammenfassung

Die vorliegende Arbeit zeigt das komplexe Zusammenspiel der Geburtsmedizin und der Pränataldiagnostik, was eine personalisierte und risikoadaptierte Betreuung von Schwangeren ermöglicht. Es besteht ein breites Wissen über Risiken und mögliche Komplikationen.

Die Demographie der Schwangeren hat sich durch das Hinzukommen von verschiedenen Risiken gewandelt: unter anderem steigendes Alter der Mütter, erhöhte Rate an Übergewicht und Adipositas sowie vermehrte Gewichtszunahme und Frauen mit einer Uterusnarbe, wie nach einem Kaiserschnitt und anderen Eingriffen. Die Vorsorge und die Beratung bei Schwangeren mit bestimmten Risikokonstellationen sollten angemessen und personalisiert erfolgen. Häufige Schwangerschaftskomplikationen wie der GDM können besser eingeschätzt und betreut werden, wenn bestimmte Eigenschaften berücksichtigt werden (zum Beispiel metabolische Typen).

Die Schwangerenbetreuung geht Hand in Hand mit der Ultraschalldiagnostik. Zur Vorsorge gehören die drei Screeninguntersuchungen, die vom G-BA vorgesehen sind. Zusätzlich kann eine weiterführende pränataldiagnostische Untersuchung angeboten werden: das Ersttrimesterscreening und die Feindiagnostik. Der differenzierte Ultraschall kann im ersten Trimester weiterführend dazu dienen, die fetale Anatomie und das Wachstum zu

untersuchen, die Wahrscheinlichkeit für eine Trisomie 21, 13, 18 zu berechnen und mögliche Schwangerschaftsrisiken wie die Präeklampsie festzustellen. Bestimmte identifizierte Risiken wie die Präeklampsie können durch die 150-mg-Gabe von Aspirin adressiert werden und erfahren damit eine Risikoreduktion. Zur differenzierten sonographischen Beurteilung stehen zahlreiche Möglichkeiten der 3D- und 4D-Sonographie zur Verfügung. Zusätzlich können Volumina mit Hilfe computerisierter automatischer Messung verarbeitet werden. Die KI-basierte Anwendung kann Standardebenen generieren, die zur Beurteilung der relevanten Strukturen genutzt werden (zentrales Nervensystem, Echokardiographie, erstes Trimenon), was die Detektion von fetalen Anomalien erleichtert.

Bei einer fetalen Fehlbildung werden weiterführende Untersuchungen angeboten, um eine mögliche Ursache zu klären. Zur Beurteilung des fetalen Karyotyps steht der NIPT zur Verfügung und kann zusätzlich nach Beratung angeboten werden. Die genetischen Untersuchungen erfolgen stufenweise und nach genetischer Beratung der werdenden Eltern: Karyotyp, ggf. Mikroarray, Trioexom. Mit jeder dieser Stufen können spezifische genetische Besonderheiten identifiziert werden: Aneuploidie, Strukturvarianten, monogene Erkrankungen. Welche Analysen durchgeführt werden, richtet sich nach dem fetalen Phänotyp und den Wünschen und Bedürfnissen der Eltern. Es existiert ein enormer Wissenszuwachs bezüglich seltener fetaler Erkrankungen und des entsprechenden fetalen Phänotyps und Genotyps. Auf dieser Grundlage können die werdenden Eltern hinsichtlich Prognose und Wiederholungswahrscheinlichkeit beraten werden.

Um die Betreuung der Schwangeren und ihrer ungeborenen Kinder personalisiert und risikoadaptiert zu intensivieren und zu verbessern, steht eine Vielzahl an Untersuchungsmethoden zur Verfügung. Vor allem die Anwendung von komplexer genetischer Diagnostik und KI entwickelt sich rapide und ist aus der Schwangerenbetreuung nicht mehr wegzudenken.

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7 Eidesstattliche Erklärung

Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass - weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde, - die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden, - mir die geltende Habilitationsordnung bekannt ist. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Berlin, den 06. Dezember 2023

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