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Commentary

The tip of the reproductive screening iceberg: 'Every mother and every fetus matters'

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Abstract

Introduction: This commentary expands on the routine pregnancy screening recommended during pregnancy, with genomic diagnosis and treatment following a positive fetal screening test indicating possible morbidity. **Materials and Methods**: Evidenced-based review article. **Results/Discussion**: An evidenced-based tool is identified for preconception risk assessment for maternal education; clinical service prioritization is promoted allowing for the ethnic and effective care for reproductive and pediatric care services; tertiary fetal diagnostic and treatment options are summarized; fetal therapy, as a quaternary service, is reviewed; human resource training is discussed. Fiscal considerations and barriers for fetal genomic and congenital malformation treatment are discussed. **Conclusion:** Prioritized healthcare service, preconception risk estimate counselling, genomic diagnosis, and fetal therapy for congenital malformations can reduce the neonatal and childhood morbidity but there may be fiscal and access to care barriers for many families.

Keywords: Maternal screening, Parental screening, Fetal screening, Neonatal screening, Reproductive screening, Diagnosis, Treatment, Malformation, Metabolic, Chromosomal, Informed consent, Informed choice, Fetal therapy, Neonatal therapy

Introduction

The basic maternity preventive, diagnostic, and treatment services support for the 'beginning of life' are routinely offered, as outlined in the 'Every Mother and Every Fetus Matters' manuscript. The routine maternity screening tests are important and necessary but if the fetal screening or imaging procedures identifies fetal pathology, the routine maternal screening tests are only the tip of the screening and diagnostic iceberg [1].

This commentary will discuss an education tool to assist in patient counselling re estimation of pregnancy morbidity to assist with appropriate maternity care triage, clinical services prioritization, and the anticipated screening and diagnostic care to evaluate for maternal and / or fetal – neonatal morbidity.

The evidenced-based tool to estimate for pregnancy morbidity

The question of 'what do women need to know and understand about childbirth' is an important one to open the dialogue between patients and providers about the severe maternal morbidity (SMM) regarding the level of maternity care choices, informed consent, understanding of the pregnancy-related risks, and the enhancement for maternal safety. When pre-conception maternal morbidity factors are present or there is a high likelihood of their occurrence, these reproductive health issues may require an informed maternity triage process with a planned or 'present' pregnancy changing from a low-risk to a complex-risk status. The 'a priori or at risk' status for either maternal

comorbidities (high body mass index; mental health issues; epilepsy; and respiratory, cardiac, gastrointestinal, renal, endocrine, fertility, or musculoskeletal disorders) or fetal conditions or both identified through the common reproductive screening processes can lead to unexpected pathologic maternal outcomes [2].

Pre-conception education for personalized maternal pregnancy risk estimates needs to be encouraged and available, given that issues related to maternal comorbidities are increasing in prevalence. The better the understanding and recognition of the maternal and pregnancy-related conditions that may change quickly from a common level of mild-to-moderate maternal morbidity to the SMM outcomes with long-term health implications, will allow for enhanced maternal education and understanding. Knowledgeable decisions, about clinical triage and maternity care with the most appropriate level of maternity provider in the appropriate maternity delivery location, are required for the best outcome. Maternal morbidity risk has increased over recent decades and these collaborative maternity care processes and discussions are required from patients, providers, and health care systems [2].

A maternal morbidity and mortality evaluation tool is available, allowing for a patient-provider review and recognition of the possible evidenced-based causes of maternal morbidity risk: pre-conception risks (maternal age >45 years; pre-existing cardiac or hypertensive conditions) and pregnancy-obstetrical risks (gestational hypertension, preeclampsia, or eclampsia; cesarean delivery, whether preterm or term; operative vaginal delivery; maternal sepsis; placenta accreta spectrum; antepartum or postpartum hemorrhage) [2].

A Clinical Service Prioritization Process

Prioritized maternal-fetal service options or choices (+/- public and private fiscal barriers) are available through multidisciplinary institutions with maternal-fetal-medicine- neonatology tertiary and quaternary services / programs. In many situations, the requests for these quaternary services are patient driven, after the patient has had maternal-fetal counselling with informed consent. Certain complex prioritized investigations or care services may not be clinically supported or available through many local maternity care institutions.

The Oregon Plan has a rigorous prioritization process that considers the conditions diagnostic-treatment needs as a pair. The ranking calculation-equation starts with *nine* consensus-based clinical care categories, then follows with *five* clinical and social impact measures, then adds a service effectiveness ranking (0-5) and finally, there is a binary service provision assessment (yes-1 or no-0) [3].

The Oregon Plan consensus-based process prioritizes 650 condition-treatment pairs, with the top 1-100 condition-treatment pairs after using the clinical consensus categories: maternity-newborn – 100 / Prevention (primary-secondary) 95 /chronic disease 75/ reproductive services 70, and then the variable impact measures ratings (adds to healthy life (0-10); tertiary prevention (0-5); impact on suffering (0-5); public population health (0-5); vulnerability of population (0-5)) [3].

The implementation of a prioritization process with team-based care for screening / preventive and diagnostic reproductive services will be the main focus for this commentary but certain tertiary-quaternary treatment options or services will be identified.

Service prioritization processes differs between the Canadian-provincial and USA healthcare systems

Clinical prioritization should be a required procedure process for healthcare services that have fixed and directed budgets for service provision. This recommendation for use with fixed funding budgets allows for the implementation / coverage for the most cost and outcome effective services. This directed recommendation could include all the provincial / territorial healthcare system in Canada while for the USA, federal Medicaid / Medicare services via each state. A clinical prioritization process can also be used for new innovative healthcare services, introduced to attract new patients and funding to a healthcare system. In the USA, the patient is a fiscal asset as they bring funding to the healthcare system for their required care while in Canada, the patient provides no additional fiscal asset to the hospital system, only to the clinical provider. The ability, therefore, to create a fetal therapy center differs between the USA and Canada as in the USA a fetal therapy service can be created with a business plan that identifies a clinical service asset with potential funding sources while in Canada service support would need to be available or re-allocated for a new hospital service which then competes with many other hospital departmental requests.

Additional Maternal- Fetal Evaluation and Treatment Options

There are numerous clinical opportunities for fetal and neonatal cohort screening to improve and increase healthy pregnancy outcomes (maternal-neonatal) and to reduce pregnancy related maternal and neonatal morbidity - mortality. There are important social, ethical, and fiscal considerations for the use of new evidenced-based maternal -fetal-neonatal genetic screening options, potential neonatal (fetal) gene therapy, maternal-fetal surgery for selected congenital anomalies, and the use of innovative extreme preterm birth / neonate treatment options (morbidity reduction) when required.

Comprehensive and multidisciplinary reproductive care programs will be considered to evaluate, counsel, and offer:

- maternal (paternal) genetic carrier screening (preconception risk prediction; antenatal identification of fetal genetic disease; triage for neonatal treatment options) [25,26].
- maternal fetal prenatal chromosomal and genomic screening and diagnostic testing with selected treatment [2-5].
- maternal obstetrical screening to prevent / moderate severe hypertensive disorders of pregnancy (early onset pre-eclampsia); maternal screening for preterm birth, with risk prediction and treatment / management [2,6-15].
- maternal-fetal surgery (open; percutaneous) for selected complex fetal anatomical malformations; monochorionic twinning congenital morbidity with congenital malformations / twin to twin transfusion syndrome (TTTS) [2,16-24].
- genomic sequencing (GS) technology has created a significant clinical opportunity for novel molecular identification for increasing numbers of monogenic disorders. The availability of GS, in diagnostic antenatal and pediatric clinics, has become the required diagnostic tool of choice, after the exclusion of other common genetic conditions. The presentation of fetal-pediatric patients with significant genetic anomalies-physiology signs (3-8%), will diagnose genetic malformations (inherited or de novo etiology) in addition to other disruptive or deformation birth defect mechanisms [30-35].

- new innovative neonatal treatment programs and options (*ex utero* aqueous support systems for the treatment of the extreme preterm delivery (22-24 weeks) [36].

The Diagnostic Testing Options following a Positive Fetal Screening Result

Pregnancy surveillance and care will identify both urgent and non-urgent care requirements as highlighted in 'Every Mother and Every Fetus Matters' while the focused genetic screening process will identify mothers and / or fetuses that require urgent evaluation or care. The healthcare center's ability to perform urgent maternal and fetal screening evaluation and diagnosis is generally available at designated regional centers but the treatment option may be limited to only delivery and postnatal maternal and neonatal management [1].

The ability, after the prenatal evaluation and diagnosis, to counsel and provide prenatal fetal therapy is a limited clinical resource and may require access to certain designated regional centers in the USA and more limited centers in Canada.

The clinical support for these genomic and 'life changing' pregnancy services have significant financial barriers, in both the public and private healthcare systems. In Canada, routine aneuploidy screening is provided with the use of variable screening algorithms by provincial screening programs with a second stage maternal serum cell-free DNA for positive 'first stage' results but industry -based private pay access for the purchase of first-tier maternal serum cell free DNA screening (NIPS by chromosome counting or single nucleotide polymorphisms technology) is available for urban patients. In the USA, similar first-tier screening technology (cell- free DNA) is offered with private pay or insurance-based arrangements through hospital or clinic-based care services [6-8].

For fetal cell free DNA screen positive cases, subsequent diagnostic testing of the fetal specimens (amniotic fluid; placental tissues; blood) is by using a chromosome micro-array to identify chromosomal aneuploidy or copy number variants [9,10].

Prenatal genomic parental and fetal testing (trios) has expanded the potential diagnostic information for fetal anatomical or physiologic pathology after testing has ruled out aneuploidy and / or CNVs as an etiology. This complex genomic evaluation requires that the fetal exome sequencing process is analyzed as 'trios' with the two parental and fetal samples [11-13].

A new concept 'Sequential perinatal carrier screening'

This genetic carrier screening concept proposes an integration of the three separate gestational times for genetic carrier screening, pre-conception, post-conception, and neonatal. The important evidence supporting this concept, is that neonate treatment for many genetic -metabolic conditions is improving. A genetic-metabolic list of neonatal conditions with neonatal treatment scores of >8.5 (best outcome score =13) identifies 35 conditions with evidenced-based good outcome morbidity from a total of 48 conditions. An ongoing requirement for this option requires a designated, frequently updated, clear, evidenced-based list for the perinatal screened fetal-neonatal conditions with quality neonatal treatment options but in addition those without good quality or adequate treatment options for palliative care choices. This concept supports patient autonomy and shared decision-making by proposing five Maternal-Fetal-Neonatal Genetic Screening pathways:

- Pathway 1 is the most limited screening option with gestational maternal-fetal well-being ultrasounds only (fetal dating 10-11 weeks; fetal anatomy 16-20 weeks; fetal growth 28-34 weeks)

- Pathway 2 has fetal aneuploidy screening for trisomy 21,18,13 and congenital malformation screening (genetic and non-genetic) only, plus Pathway 1

- Pathway 3 has enhanced fetal screening beyond aneuploidy for 4-13 genetic fetal conditions plus Pathways 1-2

- Pathway 4 has a parental-fetal process to use, if desired, a preventive genetic carrier screening paradigm approach when using genetic carrier screening in either pre or post conception with neonatal treatment as an option

- Pathway 5 has a Fetal-Neonatal plan to use a neonatal treatment directed paradigm approach regardless of the gestational time of carrier testing (pre, post, neonatal)

Collaborative processes with directed protocols will be required for this type of screening concept to be implemented (clinical service prioritization with patient -focused approach, fiscal support, carrier screening panel ≥ 176 conditions, personal or couple carrier screening at ages 20-30 years with their informed consent, for positive diagnostic fetal cases opportunity for preventive options, neonatal treatment or palliative care with collaborative delivery and fiscally supported locations, scheduled, urgent, emergent reproductive care) [37].

The Tertiary-Quaternary Clinical Care Step

The North American Fetal Therapy Network (NAFTNet) was initially created in 2004 bringing together fetal therapy programs from the USA and Canada. This group has continued to expand over the last two decades [38].

In August 2004, the National Institutes of Health organized a 'Workshop on Fetal Therapy' to develop a plan for the maternal-fetal, surgical, and neonatal evaluation and treatment of pregnancies that might benefit from in-utero therapy. At the completion of the workshop several recommendations were made, foremost of which was the 'formation of a cooperative group of clinical investigators to help set a national agenda for research and clinical progress in the field of fetal therapy'. A multi-centered fetal therapy collaborative group had previously met, to initiate and foster collaborative research between active fetal diagnosis and treatment centers in both the USA and Canada, to develop a peer review mechanism for study proposals, to explore ways to centralize data collection and study development, and to establish an educational agenda for medical professionals and the public as well as training of future surgical leaders in the field [38].

From the beginning, the USA institutions were usually private university-affiliated hospitals / departments (obstetrics, pediatrics- neonatology, pediatric surgery, anesthesia, medical genetics) with a variety of salary-based remuneration models created from departmentally shared, bundled or fee for service funding arrangements from US private insurance plans while the Canadian centers were public university-based centers limited to public-based fee for service funding from their provincial government-based systems.

The US private insurance funding process and the much larger pool of philanthropic / charitable opportunities allowed a greater USA service expansion of individual treatment / therapy centers and allowed for an increasing fiscal business opportunity for specific regional hospital -university services with experienced maternal-fetal-medicine, pediatric, and neonatology providers. In Canada, there was limited support from pediatric charitable sources and other charitable sources for reproductive obstetrical-maternity services. The provincial financial funding models generally initially limited the Canadian centers to screening and diagnostic services with percutaneous ultrasound guided procedures and endoscopic directed twin monochorionic morbidity treatment, but overtime Toronto was able to develope a full-service fetal therapy program for Canada.

There are continuing discussions, within NAFTNET members, related to voluntary regulatory and oversight agreements. A consensus statement was published to provide a framework for fetal therapy center requirements: a dedicated operational infrastructure and necessary resources to allow for appropriate oversight and monitoring of clinical performance and to facilitate multidisciplinary collaboration between the relevant specialties. Three care levels for fetal therapy centers are proposed to match the anticipated care complexity, with appropriate resources to achieve an optimal outcome at an institutional and regional level [39]:

- A level I fetal therapy center should be capable of offering fetal interventions that may be associated with obstetric risks of preterm birth or membrane rupture but that would be very unlikely to require maternal medical subspecialty or intensive care, with neonatal risks not exceeding those of moderate prematurity.

- A level II center should have the incremental capacity to provide maternal intensive care and to manage extreme neonatal prematurity.

- A level III therapy center should offer the full range of fetal interventions (including open fetal surgery) and be able manage any of the associated maternal complications and comorbidities, as well as have access to neonatal and pediatric surgical intervention including indicated surgery for neonates with congenital anomalies.

Human Resources / Training

There is no 'formal accredited' residency or fellowship training program to-date but tertiary-quaternary fetal therapy clinical service requires multi-disciplinary clinical providers for their fetal therapy evaluation and treatment services. The fetal therapy service group requires clinical expertise in maternal-fetal-medicine, imaging (ultrasound, MR), medical genetics, pediatric surgery, other pediatric subspeciality (cardiology, neurosurgery, urology), adult and pediatric anesthesia, neonatology, social work, and nursing. Each of these expert clinical providers requires a minimum of 7-8 years after their medical school training, to be able to provide this fetal therapy team-based care. The 24/7 complex maternal-fetal management service requires a human resource cohort to cover the selected labor -delivery cases along with scheduled and unscheduled procedures and surgeries. The access for an 'apprentice-model' provider training program has greater availability and opportunity through the USA NAFTNet centers, while Canada has a single quaternary NAFTNet training site in Toronto. The clinical volumes for the various these fetal surgeries are important for maintenance of skills for the team-based competence and effectiveness as well as training opportunity [38].

Discussion

The clinical service prioritization process for healthcare is an important first step but other clinical human resource synergies are required with primary and specialist providers and public health. There is a new awareness that enhanced public health services are required. Public healthcare partnerships have been shown to improve routine healthcare delivery. Perinatal quality collaboration is a critical aspect of public health infrastructure in many states and provinces. Their synergy with the healthcare system supports quality-improvement efforts in obstetrics by providing maternal health data and support for systems-level collaborative changes. Supporting these three components for public health and healthcare integration can lead to more collaborative successes [40]:

- Real-time bidirectional sharing and use of public health and healthcare data is important for providing reactive responses to changing health concerns.

- The public health and health care sectors need to identify collaborative priorities and initiate shared support.

- Clear roles and responsibilities with shared accountability will be required for an effective team-based process.

An important reproductive consideration for the public funded state or provincial/territorial healthcare systems or privately funded insurance systems, is to consider or implement, a prioritized clinical healthcare service program for support and access with ethical, preventive, treatment impact and outcome-based considerations. Health outcomes and particularly reproductive health outcomes are, at times unpredictable but by having prioritized service access and using pre-conception (preferably) or post-conception evaluations, the maternal and fetal risk estimates can be determined and shared for informed patient- centered care, based on clinical evidence [3].

There are ethical challenges for expanding the applications of clinical genetic testing. Initially, the use of genetic testing with its ethical counselling complexities were managed completely by medical geneticists and genetic counselors, but with the growing number of genetic testing choices, the patient counselling and ethical understanding is becoming a concern for more primary and specialist clinicians [41,42].

Patient access for and equity-oriented training for complex genetic reproductive screening will be required by primary and maternity care providers to discuss potential clinical disparities and patient choice prior to implementing the test. It is important for counselling providers to understand that there are inequities in the genetic databases used to validate the test results as [41,42]:

- Multiculturalism has resulted in racial and ethnic identity that does not correspond in predictable ways with the genetic ancestry.

- There is an underrepresentation of non-European genetic cohorts which leads to clinical situations that patients, from underrepresented ancestral cohorts, are more likely to have variants of unknown significance in the tested database disease- linked genes.

- Clinical polygenic risk test scores using populations with European ancestry will underestimate the risk in patients from other genetic backgrounds.

The use of genomic screening and diagnostic approaches in

under-represented clinical groups can potentially overtime provide more evidence to assist in minimizing the previously recognized health disparities.

A NEJM Editorial 'Extending Gene Medicines to All in Need' has highlighted that increasing numbers of gene therapy protocols have shown that the emergence of innovative therapies can dramatically enhance the quality and duration of life for potentially large clinical cohorts. These genomic therapies are significant scientific and clinical advances, but they are inaccessible to most people, even in high-income countries. The cost inequity issues for genomic healthcare continues but there needs to be discussions to allow countries the ability to provide scientific and fiscal incentives for the development of these innovative treatment procedures that are effective and safe but accessible and affordable [43].

The need to engage all key stakeholders (governments; biotechnology and pharmaceutical companies; researchers; regulators; patients; healthcare providers) and to find an agreement or opportunity that these innovative therapies can be made available to all patients, who might need and use them. Global distribution of these gene therapies against common diseases could be facilitated by regulatory harmonization for clinical development and licensing of gene therapies against these common diseases. Guidelines for genomic teams should be developed to help indicate what are the minimal expectations of a target product profile, with a regulatory goal for approvals in multiple regions of the world [43].

The personal, ethical, and financial barriers are just as large, for families. After the prenatal diagnosis of severe fetal morbidity and with informed consent, the family choices are between pregnancy termination or the understanding of the neonatal-childhood risk for some level of continued morbidity following the fetal therapy procedures (structural surgical repair / genomic therapy) while requiring the ongoing pediatric care and expense (dependent on health service or insurance coverage). In addition, there are many personal and systematic obstacles to consider prior to final decisions: access to abortion, if desired and available; the fetal gestational age at diagnosis; geographic factors for the family regarding their home location and their access or distance to the fetal therapy-pediatric care location(s); the variable impact on other family members / siblings; the family financial- insurance status and the clear understanding of the recurrence risks for additional pregnancies. The complexity and understanding of the decisions and choices, even with the evidenced-based risk-benefit predictions, is beyond most parental and family members.

Conclusion

This Commentary goes beyond the routine maternity care screening protocols and focuses on the positive fetal 'at risk' morbidity. The opportunity, counselling, and patient informed consent processes for enhanced genetic carrier screening, genomic fetal diagnostic testing for fetal exome (genome) sequencing, and the various treatment options for congenital malformations or genetic metabolic disease. Public and insurance healthcare programs with individual, family or group support methods are required for patient access, fiscal barriers, and personal well-being. Institutional fetal therapy regulatory and clinical outcome oversight is voluntary and collaborative, at the present time. The diagnostic and treatment for fetal and neonatal disease is advancing quickly but the present and potential cost of care is a barrier to reproductive patient-family equity and fairness when true maternal or fetal morbidity is a risk.

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